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(54) Title  
**NEW BENZIMIDAZOLE DERIVATIVES, THEIR PREPARATION PROCESS, THE NEW INTERMEDIATES OBTAINED, THEIR USE AS MEDICAMENTS AND THE PHARMACEUTICAL COMPOSITIONS CONTAINING THEM**

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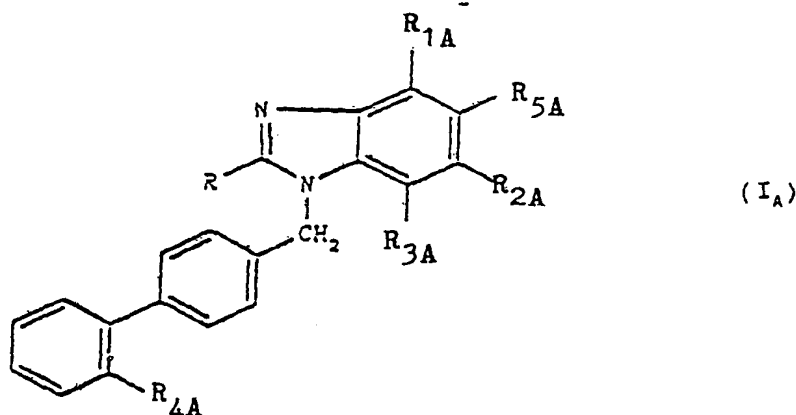
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(57) Compounds are angiotensin II inhibitors.

## CLAIM

1) Products of formula (I<sub>A</sub>):



in which:

**R represents a linear or branched alkyl or alkenyl radical**

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containing 3 or 4 carbon atoms,

$R_{1A}$ ,  $R_{2A}$ ,  $R_{3A}$  and  $R_{5A}$  are such that:

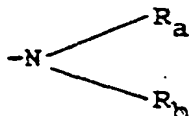
either  $R_{1A}$ ,  $R_{2A}$ ,  $R_{3A}$  and  $R_{5A}$  are identical and represent a hydrogen atom,

or  $R_{2A}$  and  $R_{5A}$  are such that one represents a hydrogen atom or a  $-\text{CH}_2-\text{O}-R_{10}$  radical, in which  $R_{10}$  represents a hydrogen atom or a linear or branched alkyl or alkenyl radical containing at most 5 carbon atoms, and the other represents a hydrogen atom, and  $R_{1A}$  and  $R_{3A}$  are such that one represents a hydrogen atom and the other is chosen from the radicals  $-\text{OR}_6$ ,  $-\text{CO}_2R_7$  and  $-\text{R}_{11}$ , in which radicals:

$R_6$  and  $R_7$ , identical or different, represent a hydrogen atom or a linear or branched alkyl or alkenyl radical containing at most 5 carbon atoms,

$R_{11}$  is chosen from the group formed by:

- a) alkyl radicals having at most 4 carbon atoms, optionally substituted by one or more radicals chosen from:
- halogen atoms,
  - the optionally acylated hydroxyl-radical,
  - linear or branched alkyloxy or alkenyloxy radicals having at most 5 carbon atoms,
  - the free, esterified or salified carboxy radical,
  - the radical:



in which  $R_a$  and  $R_b$ , identical or different, are chosen from hydrogen atoms, alkyl or alkenyl radicals having 1 to 4 carbon atoms optionally substituted by a halogen atom or a hydroxy radical,

b) linear or branched alkenyl radicals having 2 to 5 carbon atoms,

c) acyl radicals having 2 to 7 carbon atoms and the formyl radical,

$R_{4A}$  represents a free, esterified or salified carboxy radical, a cyano radical, or a tetrazolyl radical, optionally salified,

with the following provisos:

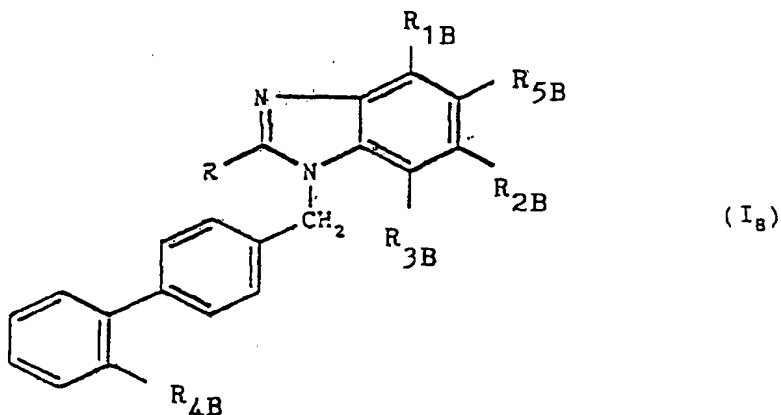
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- (1) that when R is butyl and  $R_{4A}$  is  $-CO_2H$  or 2-tetrazolyl then  $R_{3A}$  is other than hydrogen; and
- (2) when  $R_{4A}$  is t-butyloxycarbonyl or 1-(triphenylmethyl)-tetrazolyl, then
- (a)  $R_{1A}$ ,  $R_{2A}$ ,  $R_{3A}$ , and  $R_{5A}$  may not all be hydrogen
- (b) if three of  $R_{1A}$ ,  $R_{2A}$ ,  $R_{3A}$ ,  $R_{5A}$  are hydrogen the other may not be alkyl optionally substituted by hydroxy, alkoxy, amino, alkylamino and dialkylamino; alkoxy; or acyl
- (c) if two of  $R_{1A}$ ,  $R_{2A}$ ,  $R_{3A}$ ,  $R_{5A}$  are hydrogen then the other two may not simultaneously be alkyl optionally substituted by hydroxy, alkoxy, amino, alkylamino and dialkylamino; alkoxy; or acyl;
- and (3) when R is butyl and  $R_{1A}$ ,  $R_{2A}$ ,  $R_{3A}$ ,  $R_{5A}$  are all hydrogen, then,  $R_{4A}$  is not  $-CO_2CH_2CH_3$ .

6 ) Methyl 4'-[(2-butyl-1H-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate hydrochloride.

7 ) Preparation process for products of formula (I<sub>B</sub>)



in which:

R represents a linear or branched alkyl or alkenyl radical containing 3 or 4 carbon atoms,

$R_{1B}$ ,  $R_{2B}$ ,  $R_{3B}$  and  $R_{5B}$  are such that:

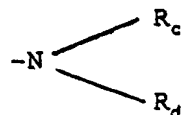
either  $R_{1B}$ ,  $R_{2B}$ ,  $R_{3B}$  and  $R_{5B}$  are identical and represent a hydrogen atom,

or  $R_{2B}$  and  $R_{5B}$  are such that one represents a hydrogen atom and the other represents a hydrogen atom or a  $-CH_2-O-R_{10}$  radical, in which  $R_{10}$  represents a hydrogen atom or a linear or

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branched alkyl or alkenyl radical containing at most 5 carbon atoms, or one of  $R_{28}$  and  $R_{38}$  represent the radical

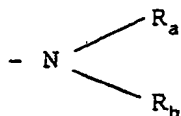


in which  $R_c$  and  $R_d$ , identical or different, represents the values defined hereafter for  $R_a$  and  $R_b$  and  $R_{18}$  and  $R_{38}$  are such that one represents a hydrogen atom and the other is chosen from the radicals  $-OR_6$ ,  $-CO_2R_7$  and  $-R_{11}$ , in which radicals:  $R_6$  and  $R_7$ , identical or different, represent a hydrogen atom or a linear or branched alkyl or alkenyl radical containing at most 5 carbon atoms,

$R_{11}$  is chosen from the group formed by:

a) alkyl radicals having at most 4 carbon atoms, optionally substituted by one or more radicals chosen from:

- halogen atoms,
- the optionally acylated hydroxyl radical,
- linear or branchedalkyloxy or alkenyloxy radicalshaving at most 5 carbon atoms,
- aryl radicals optionally substituted by one or more radicals chosen from halogen atoms, hydroxyl, trifluoromethyl, cyano, nitro, amino radicals, alkoxy radicals containing at most 4 carbon atoms, phenyl, benzyl radicals, free, salified or esterified carboxy radicals and tetrazolyl radicals,
- the free, esterified or salified carboxy radical,
- the radical:



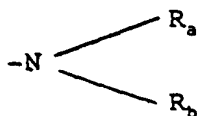
in which  $R_a$  and  $R_b$ , identical or different, are chosen from hydrogen atoms, alkyl or alkenyl radicals having 1 to 4 carbon atoms and aryl radicals, all these radicals being optionally substituted by one or more radicals chosen from halogen atoms, or the hydroxyl, trifluoromethyl, cyano, nitro or amino radical, alkoxy radicals containing at most 4 carbon atoms, phenyl or benzyl radicals, free, salified or esterified carboxy radicals and tetrazolyl radicals,

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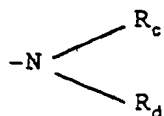
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- b) linear or branched alkenyl radicals having 2 to 5 carbon atoms,
- c) acyl radicals having 2 to 7 carbon atoms and the formyl radical,
- d) the radical:



in which  $R_a$  and  $R_b$  have the meaning indicated above,  
or one at most of  $R_{18}$ ,  $R_{28}$ ,  $R_{38}$  and  $R_{58}$  represents a hydrogen atom,

and the others are chosen from the radicals  $-\text{CH}_2-\text{O}-R_{10}$ ,  
 $-\text{OR}_6$ ,  $-\text{CO}_2R_7$ ,  $-\text{R}_{11}$  and the radical



in which  $R_6$ ,  $R_7$ ,  $R_{10}$ ,  $R_{11}$ ,  $R_c$  and  $R_d$  have the values indicated above,

$R_{48}$  represents a free, esterified or salified carboxy radical,  
or a tetrazolyl radical,

or a  $-(\text{CH}_2)_m-\text{SO}_2-\text{X}-\text{R}_{12}$  radical in which  $m$  represents an integer from 0 to 4 and

either  $(\text{X}-\text{R}_{12})$  represents  $\text{NH}_2$

or  $\text{X}$  represents a single bond, or the radicals  $-\text{NH}-$ ,  $-\text{NH}-\text{CO}-$   
 $\text{NH}-$  or  $-\text{NH}-\text{CO}-$  and  $\text{R}_{12}$  represents an alkyl, alkenyl or aryl  
radical, these radicals being optionally substituted,

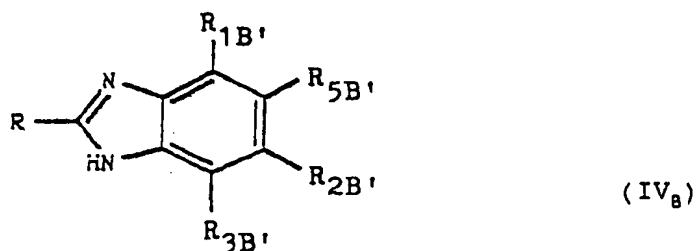
the said products of formula  $(I_8)$  being in all the possible  
racemic, enantiomeric or diastereoisomeric forms, as  
well as the addition salts with mineral or organic acids and  
mineral or organic bases of the said products of formula  $(I_8)$ .

characterized in that:

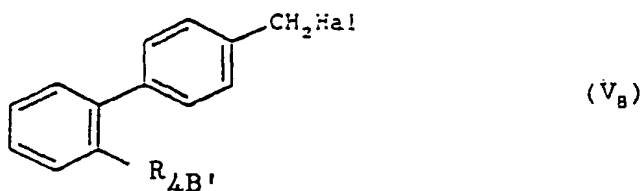
either a product of formula  $(IV_8)$ :

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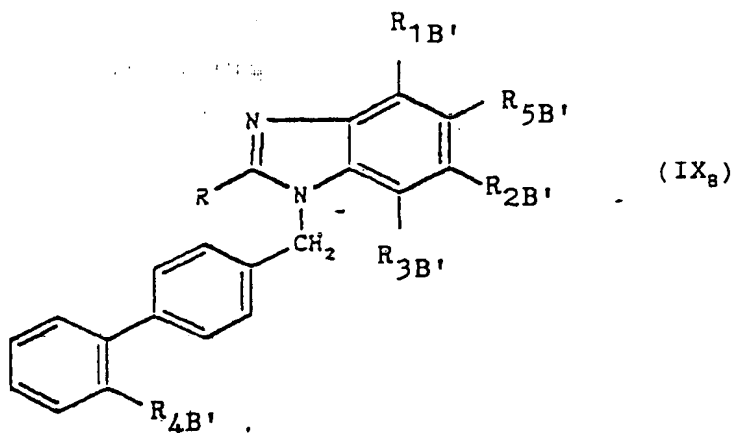
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in which R has the meaning indicated above and R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub> and R<sub>5B'</sub> have the meanings indicated above for R<sub>1B</sub>, R<sub>2B</sub>, R<sub>3B</sub> and R<sub>5B</sub> respectively in which the optional reactive functions are if desired protected by protective groups, is reacted with a compound of formula (V<sub>B</sub>):



in which Hal represents a halogen atom and R<sub>4B'</sub> has the meaning indicated above for R<sub>4B</sub> in which the optional reactive functions are, if desired, protected by protective groups, in order to obtain a product of formula (IX<sub>B</sub>):



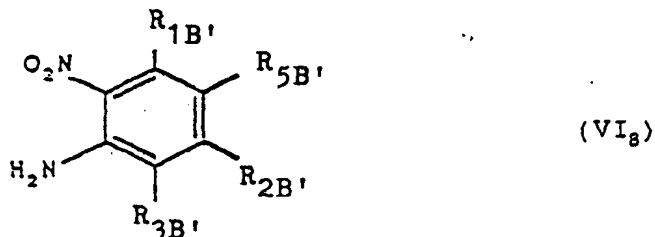
in which R, R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, R<sub>5B'</sub> and R<sub>4B'</sub> have the meanings indicated above,

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or

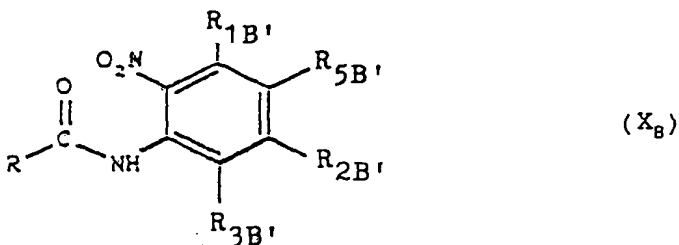
a) a compound of formula (VI<sub>8</sub>):



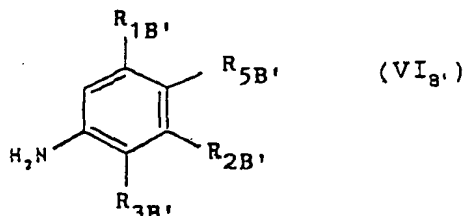
in which R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, and R<sub>5B'</sub> have the previous meanings,  
is reacted with the compound of formula (II):



in which R<sub>9</sub> represents a hydroxy or alkyloxy radical or a  
halogen atom and R has the meaning indicated above, in order  
to obtain the product of formula (X<sub>8</sub>):



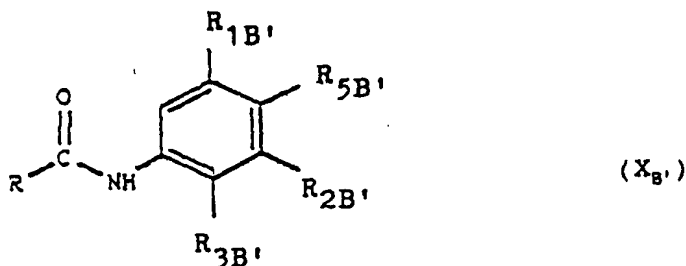
in which R, R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, and R<sub>5B'</sub> have the previous meanings,  
b) a compound of formula (VI<sub>8</sub>):



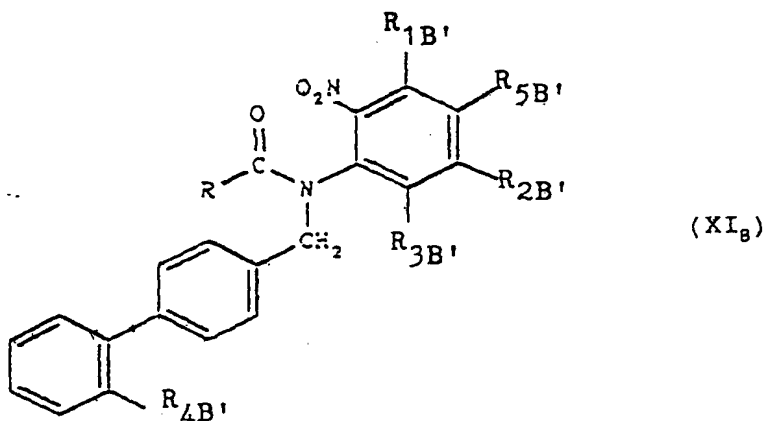
in which R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, and R<sub>5B'</sub> have the previous meanings,  
is reacted with the compound of formula (II) as defined above  
in order to obtain the product of formula (X<sub>8</sub>):

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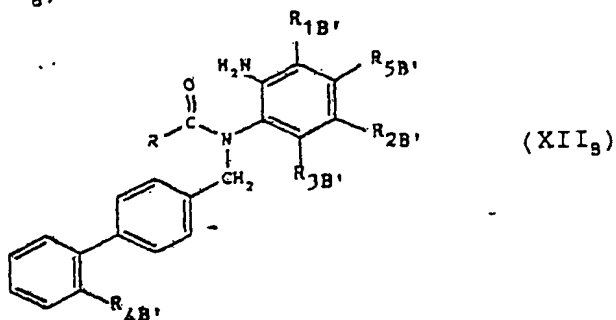
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in which R<sub>1B</sub>', R<sub>2B</sub>', R<sub>3B</sub>', R<sub>5B</sub>', and R have the meanings indicated previously,  
which is subjected to a nitration reaction in order to obtain the compound of formula (X<sub>9</sub>) as defined above,  
which product of formula (X<sub>9</sub>) is reacted with the compound of formula (V<sub>8</sub>) as defined above, in order to obtain a product of formula (XI<sub>8</sub>):



in which R, R<sub>1B</sub>', R<sub>2B</sub>', R<sub>3B</sub>', R<sub>5B</sub>', and R<sub>4B</sub>' have the previous meanings, which is subjected to a selective reduction reaction of the nitro function, in order to obtain the product of formula (XII<sub>8</sub>):



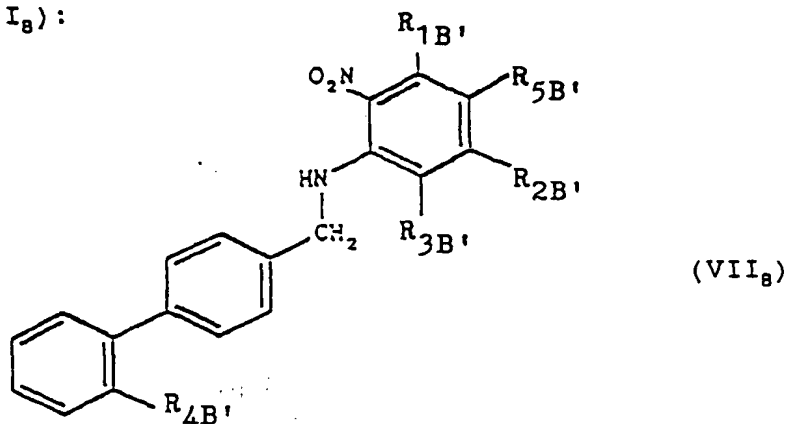


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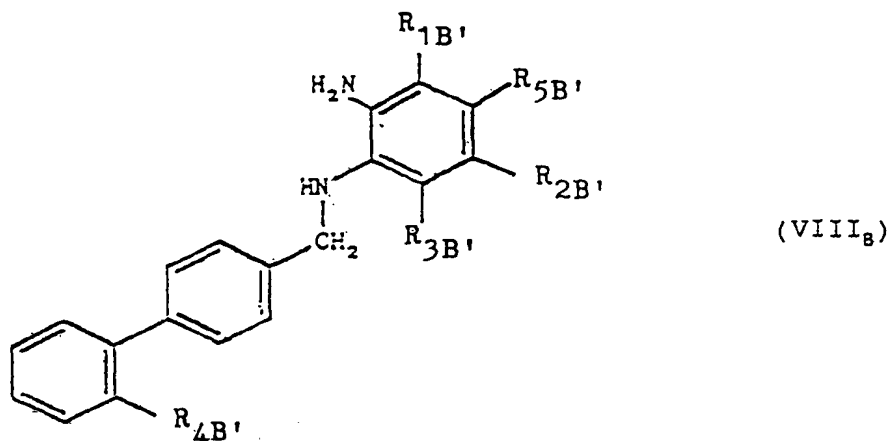
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in which R, R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, R<sub>5B'</sub>, and R<sub>4B'</sub> have the previous meanings, which is subjected to a cyclization reaction in order to obtain the products of formula (IX<sub>g</sub>) as defined above,

or the compound of formula (VI<sub>g</sub>) is reacted with the compound of formula (V<sub>g</sub>) as defined above, in order to obtain a product of formula (VII<sub>g</sub>):



in which R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, R<sub>5B'</sub>, and R<sub>4B'</sub> have the meanings indicated above, which is subjected to a reduction reaction of the nitro radical into an amino radical in order to obtain a product of formula (VIII<sub>g</sub>):



in which R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, R<sub>5B'</sub>, and R<sub>4B'</sub> have the meanings indicated above, which is reacted with the product of formula (III):



in which X represents an oxygen atom or an NH radical, R<sub>9</sub> and

R have the meaning indicated above, in order to obtain after cyclization a product of formula (IX<sub>g</sub>) as defined above, which product of formula (IX<sub>g</sub>), if desired and if necessary, is subjected to one or more of the following reactions, in any order:

- an elimination reaction of the protector groups which can be carried by the protected reactive functions,
  - a salification reaction by a mineral or organic acid or base in order to obtain the corresponding salt,
  - an esterification or salification reaction of the acid function,
  - an acid or alkaline hydrolysis reaction of the ester function into an acid function,
  - a conversion reaction of an alkyloxy radical into a hydroxy radical,
  - a conversion reaction of a haloalkyl radical into an alkylene radical,
  - a substitution reaction of a halogen atom by an amino radical,
  - a substitution reaction of a hydroxy radical by a halogen atom,
  - a reduction reaction of an esterified carboxy radical into a hydroxyalkyl radical,
  - an oxidation reaction of a hydroxyalkyl radical into an esterified carboxy radical,
  - an oxidation reaction of a hydroxymethyl radical into a formyl radical,
  - a resolution reaction of the racemic forms into resolved products,
  - a conversion reaction of a free, salified or esterified carboxy function, into a tetrazolyl radical,
- the said products of formula (I<sub>g</sub>) thus obtained being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms.

AUSTRALIA

Form 10

PATENTS ACT 1952

# COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

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Int. Cl:

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Application Number:

Lodged:

Complete Specification - Lodged:

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Published:

Priority:

Related Art:

## TO BE COMPLETED BY APPLICANT

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Complete Specification for the invention entitled:

**"NEW BENZIMIDAZOLE DERIVATIVES, THEIR PREPARATION PROCESS, THE NEW INTERMEDIATES OBTAINED, THEIR USE AS MEDICAMENTS AND THE PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"**

The following statement is a full description of this invention, including the best method of performing it known to me:-

New benzimidazole derivatives, their preparation process, the  
new intermediates obtained, their use as medicaments and the  
pharmaceutical compositions containing them.

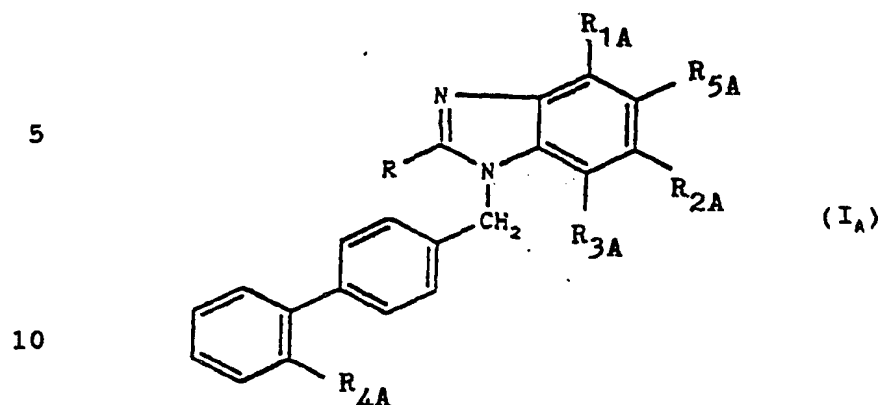
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The present invention relates to new benzimidazole  
derivatives, their preparation process, the new intermediates  
obtained, their use as medicaments and the pharmaceutical  
compositions containing them.

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A subject of the present invention is the products of  
formula (I<sub>a</sub>):





in which:

R represents a linear or branched alkyl or alkenyl radical  
15 containing 3 or 4 carbon atoms,

$R_{1A}$ ,  $R_{2A}$ ,  $R_{3A}$  and  $R_{5A}$  are such that:

either  $R_{1A}$ ,  $R_{2A}$ ,  $R_{3A}$  and  $R_{5A}$  are identical and represent a  
hydrogen atom,

or  $R_{2A}$  and  $R_{5A}$  are such that one represents a hydrogen atom or  
20 a  $-\text{CH}_2-\text{O}-R_{10}$  radical, in which  $R_{10}$  represents a hydrogen atom  
or or a linear or branched alkyl or alkenyl radical  
containing at most 5 carbon atoms, and the other represents a  
hydrogen atom, and  $R_{1A}$  and  $R_{3A}$  are such that one represents a  
hydrogen atom and the other is chosen from the radicals  $-\text{OR}_6$ ,

25  $-\text{CO}_2R_7$  and  $-\text{R}_{11}$ , in which radicals:

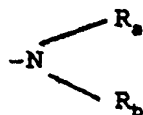
$R_6$  and  $R_7$ , identical or different, represent a hydrogen atom  
or a linear or branched alkyl or alkenyl radical containing  
at most 5 carbon atoms,

$R_{11}$  is chosen from the group formed by:

30 a) alkyl radicals having at most 4 carbon atoms, optionally  
substituted by one or more radicals chosen from:

- halogen atoms,
- the optionally acylated hydroxyl radical,
- linear or branched alkyloxy or alkenyloxy radicals having  
35 at most 5 carbon atoms,
- the free, esterified or salified carboxy radical,
- the radical:





in which  $R_a$  and  $R_b$ , identical or different, are chosen from  
 5 hydrogen atoms, alkyl or alkenyl radicals having 1 to 4  
 carbon atoms optionally substituted by a halogen atom or a  
 hydroxy radical,

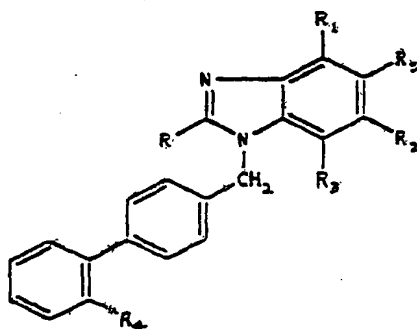
b) linear or branched alkenyl radicals having 2 to 5 carbon  
 atoms,

10 c) acyl radicals having 2 to 7 carbon atoms and the formyl  
 radical,

$R_{4A}$  represents a free, esterified or salified carboxy radical,  
 a cyano radical, or a tetrazolyl radical, optionally  
 salified, except the compounds in which  $R$  represents a

15 radical alkyl,  $R_{1A}$ ,  $R_{2A}$  and  $R_{3A}$  represent hydrogen and  $R_{3A}$   
 represents hydrogen or  $(CH_2)_n-COD$  in which  $n$  represents 0 or 1  
 and  $D$  represents hydrogen, hydroxyl, amino, alkylamino,  
 dialkylamino, halogen and alkoxy, the said products of  
 formula  $(I_A)$  being in all the possible racemic, enantiomeric  
 20 and diastereoisomeric isomer forms, as well as the addition  
 salts with mineral or organic acids and mineral or organic  
 bases of the said products of formula  $(I_A)$ .

Thus a subject of the present invention is the products  
 of formulae  $(I_A)$ , as defined above and corresponding to the  
 25 formula  $(I)$ :



(I)

in which:

$R$  represents a linear or branched alkyl or alkenyl radical  
 containing 3 or 4 carbon atoms,

35  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_5$  are such that:

either  $R_1$ ,  $R_2$ ,  $R_3$  and  $R_5$  are identical and represent a hydrogen  
 atom,

or  $R_2$  and  $R_5$  are such that one represents a hydrogen atom or a  
 $-CH_2-O-R_{10}$  radical and the other represents a hydrogen atom,

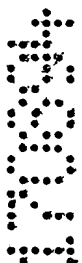
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and  $R_1$  and  $R_2$  are such that:

one represents a hydrogen atom and the other is chosen from the radicals  $-OR_6$ ,  $-CO_2R_7$  and  $-CH_2-O-R_8$ , which radicals  $R_{10}$ ,  $R_6$ ,  $R_7$  and  $R_8$ , identical or different, represent a hydrogen



atom or a linear or branched alkyl or alkenyl radical containing at most 5 carbon atoms,

$R_4$  represents a free, esterified or salified carboxy radical, the said products of formula (I) being in all the possible 5 racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral or organic acids and mineral or organic bases of the said products of formula (I).

In the products of formulae  $(I_B)$ ,  $(I_A)$  and (I) and in what follows:

- 10 - the term linear or branched alkyl radical preferably designates methyl, ethyl, propyl or isopropyl, butyl, isobutyl, sec-butyl or tert-butyl radicals but can also represent a pentyl radical and in particular tert-pentyl,
- the term linear or branched alkenyl radical preferably 15 designates a vinyl, allyl, 1-propenyl, 2-propenyl, 1-butenyl, or 2-butenyl radical but can also represent a 1-pentenyl, 2-pentenyl or also 3-pentenyl radical,
- the term halogen atom preferably designates the bromine atom, but can also represent a fluorine, chlorine or iodine 20 atom,
- the alkyloxy and alkenyloxy radicals that can be represented by  $O-R_{10}$  and  $-O-R_6$  are formed for example with the alkyl and alkenyl radicals as defined above, for alkyloxy radicals there can be mentioned preferably 25 methoxy or ethoxy radicals, but also propoxy, isopropoxy, butoxy, sec-butoxy, tert-butoxy or also pentoxy radicals, for alkenyloxy radicals there can be mentioned preferably vinyloxy or propenyloxy radicals,
- for esterified carboxy radicals, there can be mentioned 30 preferably a (lower alkyloxy or alkenyloxy carbonyl) group such as methoxycarbonyl or ethoxycarbonyl, but also propoxycarbonyl, butoxycarbonyl, butenyloxy carbonyl, tert-butoxycarbonyl, or also pentoxycarbonyl radicals,
- the term acyl radical preferably designates a radical 35 having at most 7 carbon atoms such as the formyl, acetyl, propionyl, butyryl or benzoyl radical, but can also represent a valeryl, hexanoyl, acryloyl, crotonoyl or carbamoyl radical,
- the term acyloxy radical preferably designates the groups



containing one of the acyl radicals as defined above and linked to an oxygen atom, such as for example acetoxy or benzoyloxy,

- the term aryl radical designates monocyclic radicals or
- 5 radicals constituted by condensed rings, carbocyclic or heterocyclic, it being understood that the heterocyclic radicals can contain one or more heteroatoms chosen from oxygen, nitrogen or sulphur atoms and that when these heterocyclic radicals contain more than one heteroatom, the
- 10 heteroatoms of these heterocyclic radicals can be identical or different.

The term monocyclic radical preferably designates radicals which contain 5 or 6 links, as carbocyclic monocyclic radicals, there can be mentioned the

- 15 phenyl radical;
- among the heterocyclic monocyclic radicals, there can be mentioned, for example, the following radicals: thienyl, furyl, pyranlyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl,
- 20 furazanyl, pyrrolinyl such as delta 2-pyrrolinyl, imidazolinyl such as delta 2-imidazolinyl, pyrazolinyl such as delta 3-pyrazolinyl, as well as the isomers of position of the heteroatom or heteroatoms that these radicals can contain such as, for example, isothiazolyl or isoxazolyl radicals.

- 25 The term radical constituted by condensed rings preferably designates radicals which contain 8 to 14 links:
- among the radicals constituted by carbocyclic condensed rings there can be mentioned, for example, the naphthyl and phenanthryl radicals,

- 30 among the radicals constituted by heterocyclic condensed rings there can be mentioned, for example, benzothienyl, naphtho-[2,3-b]-thienyl, thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, indolizinyll, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, quinolizinyll,
- 35 isoquinolyl, quinolyl, phthalazinyl, the naphthyridinyl, imidazopyridyl, quinoxalinyll, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, acridinyl, phenazinyl, phenothiazinyl,

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phenoxazinyl, indolinyl, isoindolinyl or also condensed polycyclic systems constituted by heterocyclic monocyclics as defined above, such as for example furo-[2,3-b]-pyrrole or thieno-[2,3-b]-furane.

5 As examples of such an aryl radical, there can be mentioned the following radicals: phenyl, naphthyl, thienyl such as thien-2-yl and thien-3-yl, furyl such as fur-2-yl, pyridyl such as pyrid-3-yl, pyrimidyl, pyrrolyl, thiazolyl, isothiazolyl, diazolyl, triazolyl, tetrazolyl, thiadiazolyl, 10 thiatriazolyl, oxazolyl, oxadiazolyl, 3- or 4-isoxazolyl; condensed heterocyclic groups containing at least one heteroatom chosen from sulphur, nitrogen and oxygen, for example benzothienyl such as benzothien-3-yl, benzofuryl, benzopyrrolyl, benzimidazolyl, benzoxazolyl, thionaphthyl, 15 indolyl or purinyl.

Such aryl radicals can be optionally substituted such as for example the N-substituted pyrrolyl radical, for example N-methylpyrrolyl, the substituted 3- or 4-isoxazolyl radical, for example, 3-aryl-5-methylisoxazol-4-yl, the aryl group 20 being, for example, a phenyl or halophenyl group; - the groups



25 which represent an amino radical optionally substituted by one or two identical or different radicals, designate for example monoalkyl and dialkylamino radicals in which the alkyl radicals can take the meanings indicated above, such as for 30 example, methyl, ethyl, isopropyl, butyl, isobutyl, these radicals being optionally substituted, such as for example in hydroxymethyl, hydroxyethyl, methoxymethyl, methoxyethyl or also ethoxyethyl, trifluoromethyl, pentafluoromethyl; the amino radical can also be substituted by one or two alkenyl 35 radicals as defined above and such as for example vinyl, allyl, 1-propenyl and 1-butenyl radicals; among the substituents of these amino radicals, there can also be mentioned aryl and aralkyl radicals such as, for example,

the following radicals: phenyl, benzyl, phenethyl, naphthyl, indolyl, indolinyl, thienyl, furyl, pyrrolyl, pyridyl, pyrrolidinyl, piperidino, morpholino, piperazinyl, these radicals being able to be substituted by one or more radicals 5 as defined above, such as for example in methyl-piperazinyl, fluoromethylpiperazinyl, ethylpiperazinyl, propylpiperazinyl, phenylpiperazinyl or benzylpiperazinyl.

- the  $-(CH_2)_m-SO_2-X-R_{12}$  radical can represent for example the radicals in which  $(CH_2)_m$  represents the alkylene values of the 10 alkyl radicals indicated above such as, for example, methylene, ethylene, n-propylene, isopropylene, isobutylene or tert-butylene and  $R_{12}$  can represent an alkyl radical chosen from the values defined above, or an aryl radical also chosen from the values indicated above for this radical, such as for 15 example phenyl, biphenyl, naphthyl, tetrazolyl; the alkyl radical that can be represented by the  $R_{12}$  radical can be optionally substituted by an aryl radical chosen from the values defined above in order to form an aralkyl radical.

These alkyl, aryl and aralkyl radicals can themselves be 20 substituted as is indicated above for these radicals.

There can be mentioned, for example and in a non-exhaustive manner, the following radicals:  $-SO_2-NH_2$ ,  $-SO_2-NH-CH_3$ ,  $-SO_2-NH-CF_3$ ,  $-SO_2-NH-C_6H_5$ ,  $-SO_2-NH-CH_2-C_6H_5$ .

The radical R preferably represents a propyl, 1-propenyl, 25 butyl or 1-butenyl radical but can also represent an isopropyl, sec-butyl, tert-butyl and 2-butenyl radical.

The addition salts with mineral or organic acids and mineral or organic bases of the products of formulae  $(I_B)$ ,  $(I_A)$  and (I) can be, for example, the salts formed with the 30 following acids: hydrochloric, hydrobromic, hydroiodic, nitric, sulphuric, phosphoric, propionic, acetic, formic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic, aspartic, ascorbic, alkylmonosulphonic such as for example methanesulphonic, ethanesulphonic, propanesulphonic, 35 alkyldisulphonic such as for example methanedisulphonic, 1,2-ethanedisulphonic, arylmonosulphonic such as benzenesulphonic and aryldisulphonic.

The salts formed with hydrochloric acid are notably

preferred.

The carboxy radical or radicals of the products of formula (I) can be salified by mineral bases such as, for example, an equivalent of sodium, potassium, lithium, calcium, magnesium or ammonium or organic bases such as, for example, methylamine, propylamine, trimethylamine, diethylamine, triethylamine, N,N-dimethylethanolamine, tris (hydroxymethyl) amino methane, ethanolamine, pyridine, picoline, dicyclohexylamine, morpholine, benzylamine, procaine, lysine, arginine, histidine, N-methylglucamine.



Among the products in which  $R_{1A}$  represents an alkyloxy radical, there can be mentioned for example the products in which  $R_{2A}$ ,  $R_{3A}$  and  $R_{5A}$  represent a hydrogen atom.

5 In the preferred products indicated above the alkyl and alkyloxy radicals contain 1 to 5 carbon atoms and preferably represent respectively:

- for the alkyl radicals, ethyl and methyl radicals,
- and for the alkyloxy radicals, methoxy and ethoxy radicals.

10 A quite particular subject of the invention is the products of formula (I<sub>A</sub>) as defined above, in which R represents a butyl radical and  $R_{1A}$ ,  $R_{2A}$ ,  $R_{3A}$  and  $R_{5A}$  represent a hydrogen atom, the said products of formula (I<sub>A</sub>) being in all the possible racemic, enantiomeric and diastereoismeric isomer forms, as well as the addition salts with mineral or organic acids and mineral or  
15 organic bases of the said products of formula (I<sub>A</sub>).

A more particular subject of the invention is the products of formula (I<sub>A</sub>) as defined above, in which R represents a butyl radical,  $R_{1A}$ ,  $R_{2A}$  and  $R_{5A}$  represent



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a hydrogen atom, and  $R_{3A}$  is chosen from the radicals  $-OR_4$ ,  
 $-CO_2R_7$  and  $-R_{11}$ , in which radicals:

$R_4$  and  $R_7$ , identical or different, represent a hydrogen atom or  
5 a linear or branched alkyl or alkenyl radical containing at

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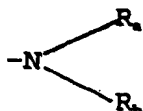


most 5 carbon atoms.

$R_{11}$  is chosen from the group formed by:

a) alkyl radicals having at most 4 carbon atoms, optionally substituted by one or more radicals chosen from:

- 5 - halogen atoms,
- the optionally acylated hydroxy radical,
- linear or branched alkyloxy or alkenyloxy radicals having at most 5 carbon atoms,
- free, esterified or salified carboxy radicals,
- 10 - the radical:



in which  $R_a$  and  $R_b$ , identical or different, are chosen from 15 hydrogen atoms, alkyl or alkenyl radicals having 1 to 4 carbon atoms, optionally substituted by a halogen atom or a hydroxy radical,

b) linear or branched alkenyl radicals having 2 to 5 carbon atoms,

- 20 c) acyl radicals having 2 to 7 carbon atoms and the formyl radical,  $R_{1A}$  having the meaning indicated above, the said products of formula  $(I_A)$  being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral or organic acids and mineral
- 25 or organic bases of the said products of formula  $(I_A)$ .

Notably a subject of the invention is the products of formula  $(I_A)$  as defined above, in which R represents a butyl radical and  $R_{1A}$ ,  $R_{2A}$  and  $R_{3A}$  represent a hydrogen atom, and  $R_{4A}$  represents hydrogen; a carboxy radical free or esterified by

30 an alkyl radical containing at most 4 carbon atoms; a formyl radical; an alkyl or alkenyl radical containing at most 4 carbon atoms; the alkyl radical being optionally substituted by one or more radicals chosen from halogen atoms, hydroxy or acyloxy radicals, amino radicals optionally substituted by one

35 or two alkyl radicals containing at most 4 carbon atoms; the said products of formula  $(I_A)$  being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with the mineral or organic acids



and mineral or organic bases of the said products of formula (I<sub>A</sub>).

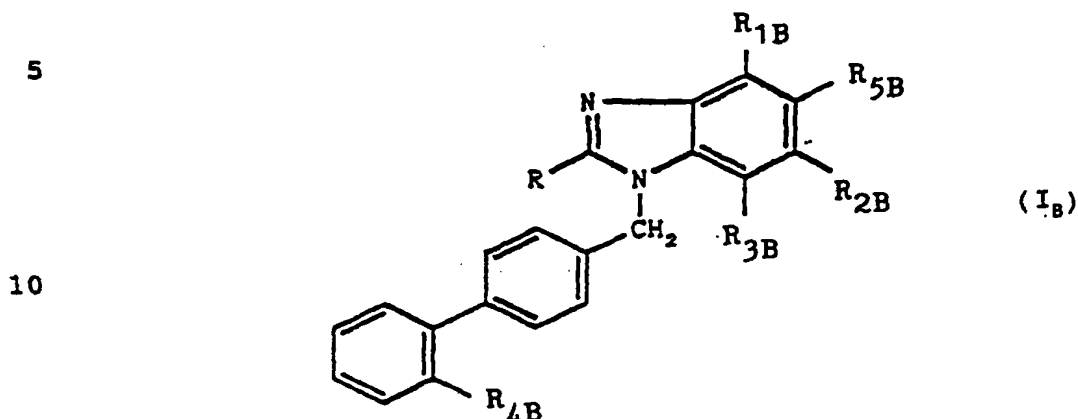
Among the products which are a subject of the invention, there can be mentioned quite particularly:

- 5 methyl 4'-[(2-butyl-1H-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate and its salts,  
4'-[(2-butyl-1H-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid and its salts,  
2-butyl-1-[(2'-carboxy-biphenyl-4-yl)-methyl]-1H-benzimidazole-  
10 7-carboxylic acid and its salts,  
4'-[[2-butyl-7-(2-hydroxyethyl)-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid and its salts,  
4'-[(2-butyl-7-formyl-1H-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid and its salts,  
15 2-butyl-1-[[2'-(1H-tetrazol-5-yl)-(1,1'-biphenyl)-4-yl]-methyl]-1H-benzimidazole-7-carboxylic acid and its salts.



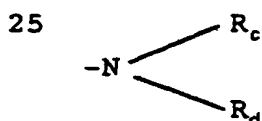


Also a subject of the invention is a preparation process for products of formula (I<sub>B</sub>)



in which:

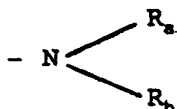
- 15 R represents a linear or branched alkyl or alkenyl radical containing 3 or 4 carbon atoms,  
 $R_{1B}$ ,  $R_{2B}$ ,  $R_{3B}$  and  $R_{5B}$  are such that:  
 either  $R_{1B}$ ,  $R_{2B}$ ,  $R_{3B}$  and  $R_{5B}$  are identical and represent a hydrogen atom,  
 20 or  $R_{2B}$  and  $R_{5B}$  are such that one represents a hydrogen atom and the other represents a hydrogen atom or a  $-\text{CH}_2-\text{O}-R_{10}$  radical, in which  $R_{10}$  represents a hydrogen atom or a linear or branched alkyl or alkenyl radical containing at most 5 carbon atoms, or one of  $R_{2B}$  and  $R_{5B}$  represent the radical



- in which  $R_c$  and  $R_d$ , identical or different, represents the values defined hereafter for  $R_a$  and  $R_b$  and  $R_{1B}$  and  $R_{3B}$  are such  
 30 that one represents a hydrogen atom and the other is chosen from the radicals  $-\text{OR}_6$ ,  $-\text{CO}_2R_7$  and  $-\text{R}_{11}$ , in which radicals:  $R_6$  and  $R_7$ , identical or different, represent a hydrogen atom or a linear or branched alkyl or alkenyl radical containing at most 5 carbon atoms,  
 35  $R_{11}$  is chosen from the group formed by:  
 a) alkyl radicals having at most 4 carbon atoms, optionally substituted by one or more radicals chosen from:  
 - halogen atoms,  
 - the optionally acylated hydroxyl radical,



- linear or branched alkyloxy or alkenyloxy radicals having at most 5 carbon atoms,
  - aryl radicals optionally substituted by one or more radicals chosen from halogen atoms, hydroxyl, trifluoromethyl, cyano, nitro, amino radicals, alkoxy radicals containing at most 4 carbon atoms, phenyl, benzyl radicals, free, salified or esterified carboxy radicals and tetrazolyl radicals,
  - the free, esterified or salified carboxy radical,
- 10 - the radical:



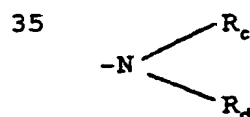
- in which  $R_a$  and  $R_b$ , identical or different, are chosen from hydrogen atoms, alkyl or alkenyl radicals having 1 to 4 carbon atoms and aryl radicals, all these radicals being optionally substituted by one or more radicals chosen from halogen atoms, or the hydroxyl, trifluoromethyl, cyano, nitro or amino radical, alkoxy radicals containing at most 4 carbon atoms, phenyl or benzyl radicals, free, salified or esterified carboxy radicals and tetrazolyl radicals,
- b) linear or branched alkenyl radicals having 2 to 5 carbon atoms,

c) acyl radicals having 2 to 7 carbon atoms and the formyl radical,

d) the radical:



- 30 in which  $R_a$  and  $R_b$  have the meaning indicated above, or one at most of  $R_{1B}$ ,  $R_{2B}$ ,  $R_{3B}$  and  $R_{5B}$  represents a hydrogen atom, and the others are chosen from the radicals  $-CH_2-O-R_{10}$ ,  $-OR_6$ ,  $-CO_2R_7$ ,  $-R_{11}$  and the radical



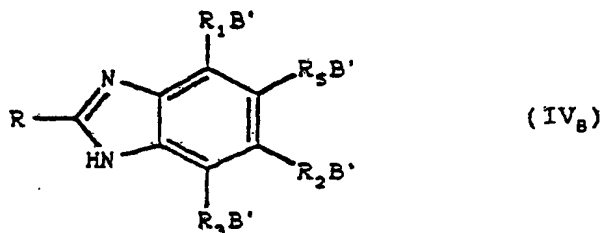
in which  $R_6$ ,  $R_7$ ,  $R_{10}$ ,  $R_{11}$ ,  $R_a$  and  $R_d$  have the values indicated above,



$R_{4B}$  represents a free, esterified or salified carboxy radical, or a tetrazolyl radical, or a  $-(CH_2)_m-SO_2-X-R_{12}$  radical in which  $m$  represents an integer from 0 to 4 and

- 5 either  $(X-R_{12})$  represents  $NH_2$  or  $X$  represents a single bond, or the radicals  $-NH-$ ,  $-NH-CO-$ ,  $NH-$  or  $-NH-CO-$  and  $R_{12}$  represents an alkyl, alkenyl or aryl radical, these radicals being optionally substituted, the said products of formula  $(I_B)$  being in all the possible  
 10 racemic, enantiomeric or diastereoisomeric forms, as well as the addition salts with mineral or organic acids and mineral or organic bases of the said products of formula  $(I_B)$  characterized in that:  
 either a product of formula  $(IV_B)$ :

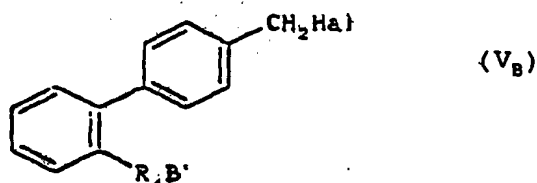
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- in which  $R$  has the meaning indicated above and  $R_{1B'}$ ,  $R_{2B'}$ ,  $R_{3B'}$  and  $R_{5B'}$  have the meanings indicated above for  $R_{1B}$ ,  $R_{2B}$ ,  $R_{3B}$  and  $R_{5B}$  respectively in which the optional reactive functions are  
 25 if desired protected by protective groups, is reacted with a compound of formula  $(V_B)$ :

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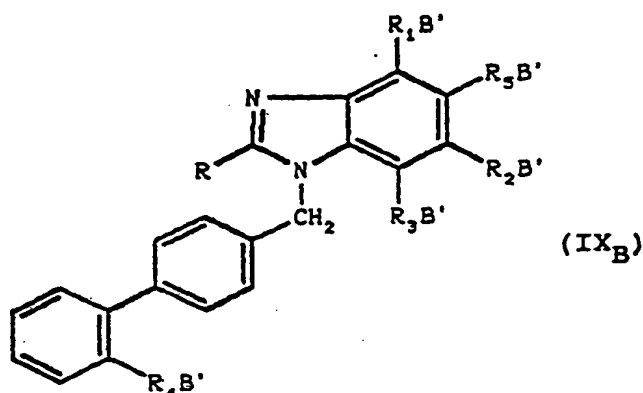
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in which Hal represents a halogen atom and  $R_{4B}$  has the meaning indicated above for  $R_{4B}$  in which the optional reactive functions are, if desired, protected by protective groups, in order to obtain a product of formula (IX<sub>B</sub>):

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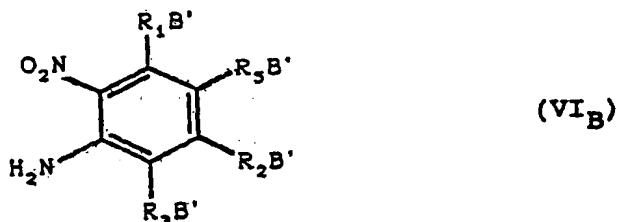
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in which R,  $R_{1B'}$ ,  $R_{2B'}$ ,  $R_{3B'}$ ,  $R_{5B'}$  and  $R_{4B'}$  have the meanings indicated above,

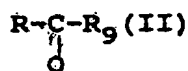
20 or

a) a compound of formula (VI<sub>B</sub>):

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in which  $R_{1B'}$ ,  $R_{2B'}$ ,  $R_{3B'}$  and  $R_{5B'}$  have the previous meanings, 30 is reacted with the compound of formula (II):

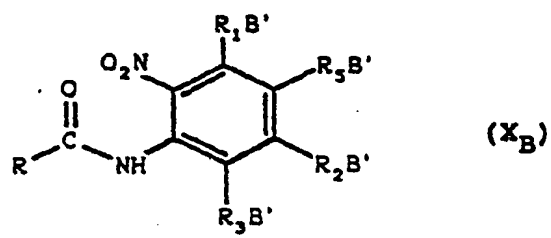


35 in which  $R_9$  represents a hydroxy or alkyloxy radical or a halogen atom and R has the meaning indicated above, in order to obtain the product of formula (X<sub>B</sub>):



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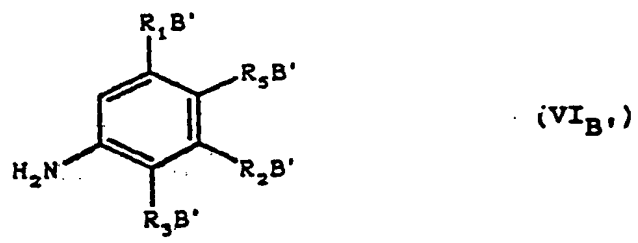
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in which R, R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, and R<sub>5B'</sub> have the previous meanings,

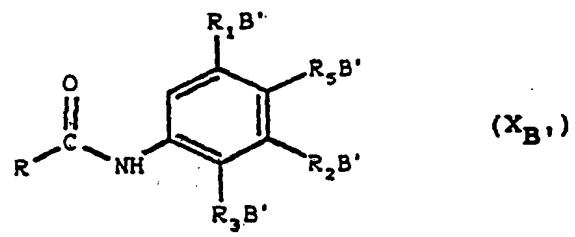
10 b) a compound of formula (VI<sub>B</sub>):

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in which R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, and R<sub>5B'</sub> have the previous meanings,  
 20 in order to obtain the product of formula (X<sub>B</sub>):

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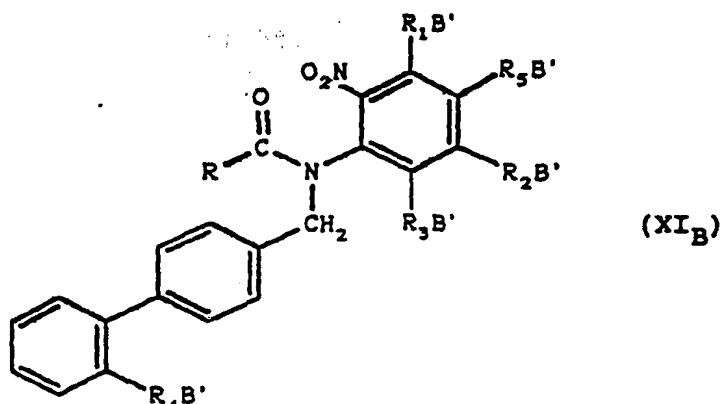
30 in which R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, R<sub>5B'</sub>, and R have the meanings indicated previously,  
 which is subjected to a nitration reaction in order to obtain the compound of formula (X<sub>B</sub>) as defined above,  
 which product of formula (X<sub>B</sub>) is reacted with the compound of  
 35 formula (V<sub>B</sub>) as defined above, in order to obtain a product of formula (XI<sub>B</sub>):



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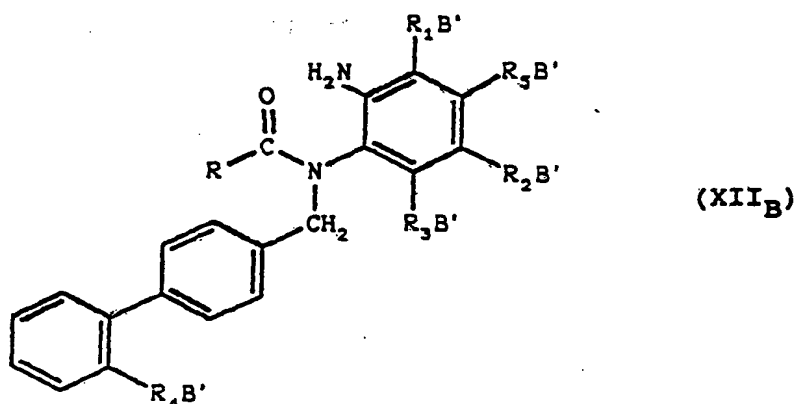
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in which R, R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, R<sub>5B'</sub>, and R<sub>4B'</sub>, have the previous meanings, which is subjected to a selective reduction reaction of the nitro function, in order to obtain the product of  
15 formula (XII<sub>B</sub>):

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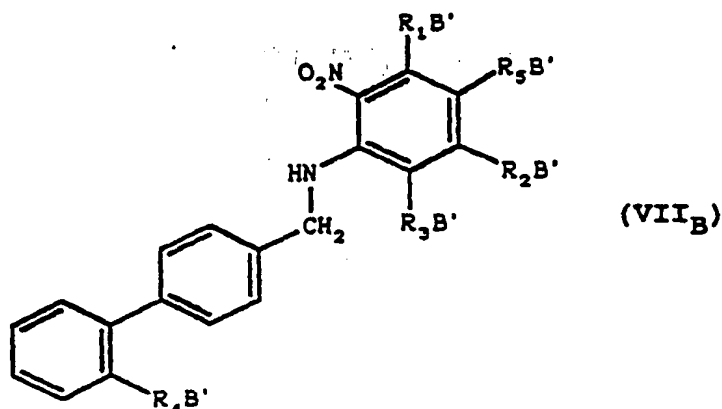


30 in which R, R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, R<sub>5B'</sub>, and R<sub>4B'</sub>, have the previous meanings, which is subjected to a cyclization reaction in order to obtain the products of formula (IX<sub>B</sub>) as defined above,  
or the compound of formula (VI<sub>B</sub>) is reacted with the compound  
35 of formula (V<sub>B</sub>) as defined above, in order to obtain a product of formula (VII<sub>B</sub>):



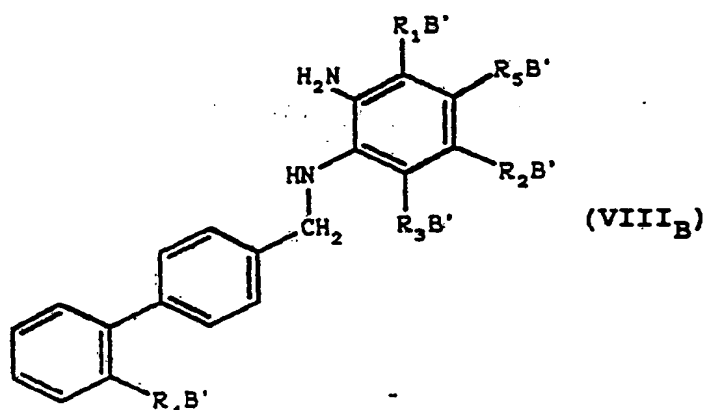
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in which  $R_{1B'}$ ,  $R_{2B'}$ ,  $R_{3B'}$ ,  $R_{5B'}$ , and  $R_{4B'}$  have the meanings indicated above, which is subjected to a selective reduction reaction of the nitro radical in order to obtain a product of formula (VIII<sub>B</sub>):

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in which  $R_{1B'}$ ,  $R_{2B'}$ ,  $R_{3B'}$ ,  $R_{5B'}$ , and  $R_{4B'}$  have the meanings indicated above, which is reacted with the product of formula (III):

30 (III):



in which X represents an oxygen atom or an NH radical,  $R_9$  and R have the meaning indicated above, in order to obtain after cyclisation a product of formula (IX<sub>B</sub>) as defined above, which product of formula (IX<sub>B</sub>), if desired and if necessary, is subjected to one or more of the following reactions, in any order:

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- an elimination reaction of the optional protector groups,
  - a salification reaction by a mineral or organic acid or base in order to obtain the corresponding salt,
  - an esterification or salification reaction of the acid
- 5 function,
- an acid or alkaline hydrolysis reaction of the ester function into an acid function,
  - a conversion reaction of an alkyloxy radical into a hydroxy radical,
- 10 - a conversion reaction of a haloalkyl radical into an alkylene radical,
- a substitution reaction of a halogen atom by an amino radical,
  - a substitution reaction of a hydroxy radical by a halogen
- 15 atom,
- a reduction reaction of an esterified carboxy radical into a hydroxyalkyl radical,
  - an oxidation reaction of a hydroxyalkyl radical into an esterified carboxy radical,
- 20 - an oxidation reaction of a hydroxymethyl radical into a formyl radical,
- a resolution reaction of the racemic forms into resolved products,
  - a conversion reaction of a free, salified or esterified
- 25 carboxy function, into a tetrazolyl radical,
- the said products of formula (I<sub>B</sub>) thus obtained being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms.

In the preferred conditions for implementing the  
 30 invention, the <sup>inventive</sup> above process is carried out in the following manner:

The reaction of the compound of formula (V<sub>B</sub>) in which the halogen atom preferably represents a bromine atom on the anion of the imidazole of formula (IV<sub>B</sub>) prepared for example by the  
 35 action of an alkaline agent such as sodium or potassium hydride or also of a sodium or potassium alcoholate such as for example sodium methylate, can be carried out, for example, in an organic solvent such as dimethylformamide or





tetrahydrofuran.

The addition reaction of the compounds of formula (II) on the free amine function of the compounds of formula (VI<sub>B</sub>) or (VI<sub>B</sub>) in order to obtain the products of formula (X<sub>B</sub>) or 5 (X<sub>B</sub>) respectively can be carried out by simple heating to a temperature of about 120°C to 170°C: a compound of formula (II) can be for example valeric acid, used in this case preferably in excess relative to the compound of formula (VI<sub>B</sub>) or (VI<sub>B</sub>).

10 The nitration reaction of the products of formula (X<sub>B</sub>) in order to give the products of formula (X<sub>B</sub>) can be carried out for example in the presence of nitric acid in a solvent such as for example acetic anhydride and acetic acid at a temperature of between 0 and 10°C.

15 The addition reaction of the compounds of formula (V<sub>B</sub>) on the amide function of the compounds of formula (X<sub>B</sub>) in order to obtain the products of formula (XI<sub>B</sub>) can be carried out at ambient temperature or by heating to a temperature of between 20°C and 150°C, preferably in the presence of an alkaline 20 agent such as for example triethylamine, soda, sodium methylate or ethylate or also sodium hydride in a solvent such as for example tetrahydrofuran or dimethyl-formamide.

The reduction of the nitro radical of the products of formula (XI<sub>B</sub>) into an amino radical in order to obtain the 25 products of formula (XII<sub>B</sub>) can be carried out according to the usual methods known to a man skilled in the art, notably by catalytic hydrogenation in the presence of palladium hydroxide in a solvent such as for example ethanol or by zinc in a solvent such as for example acetic acid in the presence of 30 sodium acetate or also by sodium borohydride.

The cyclization reaction of the products of formula (XII<sub>B</sub>) in order to obtain the products of formula (IX<sub>B</sub>) can be carried out by simple heating or in the presence of a catalyst such as for example thionyl chloride, phosphorous 35 pentachloride or also phosphoric anhydride in a solvent such as for example tetrahydrofuran or dimethylformamide.

The addition reaction of the compounds of formula (V<sub>B</sub>) on the free amine function of the compounds of formula (VI<sub>B</sub>) in



order to obtain the products of formula (VII<sub>B</sub>) can be carried out in the same conditions as those described above for the addition of the compounds of formula (V<sub>B</sub>) on the products of formula (IV<sub>B</sub>).

- 5        The reduction of the nitro radical of the products of formula (VII<sub>B</sub>) into an amino radical in order to obtain the products of formula (VIII<sub>B</sub>) can be carried out according to the usual methods known to a man skilled in the art, notably in the same conditions as those described above for the
- 10 reduction of the nitro radical of the products of formula (XI<sub>B</sub>).

      The addition reaction of the compounds of formula (III) on the free amine radical of the products of formula (VIII<sub>B</sub>) followed by the cyclization of the products thus obtained can

15 be carried out according to various reaction conditions known to a man skilled in the art, preferably in an organic solvent such as for example tetrahydrofuran or dimethylformamide at a temperature of between 20°C and 200°C.

      The compound of formula (III) can be, for example, when X

20 represents NH, ethyl pentanimidoate and when X represents O, for example, valeric acid.

      According to the values of R<sub>1B</sub>, R<sub>2B</sub>, R<sub>3B</sub> and R<sub>5B</sub>, the products of formula (IX<sub>B</sub>) constitute or do not constitute the products of formula (I<sub>B</sub>).

- 25        The various reactive functions that can be carried by some of the compounds defined above can, if necessary, be protected: they may be, for example, free hydroxy or carboxy radicals which can be protected by the easily-eliminated appropriate protective groups.

- 30        The following non-exhaustive list of examples of protection of reactive functions can be mentioned:
- the hydroxy radicals can be protected for example by trimethylsilyl, methoxymethyl or tetrahydropyranyl radicals,
  - the carboxy groups can be protected for example in the form
- 35 of esters formed with easily cleavable esters such as benzyl or tert-butyl esters or esters known in the chemistry of the peptides.

      The elimination of these protective groups can be carried



out in the usual conditions known to a man skilled in the art, notably by acid hydrolysis carried out with an acid such as hydrochloric, benzenesulphonic, paratoluenesulphonic, formic or trifluoroacetic acid.

5 A list of different protective groups which can be used will be found for example in the Patent BF 2,499,995.

The products described above can, if desired, be subjected to salification reactions by a mineral or organic acid carried out according to the usual methods known to a man  
10 skilled in the art.

The optional conversions of ester functions into an acid function of the products described above can be, if desired, carried out in the usual conditions known to a man skilled in the art, notably by acid hydrolysis with sulphuric or  
15 hydrochloric acid, or also by alkaline hydrolysis for example with soda or potash in an alcohol medium such as, for example, in methanol.

The optional alkyloxy functions such as notably methoxy of the products described above can be, if desired, converted  
20 into an alcohol function in the usual conditions known to a man skilled in the art, for example by boron tribromide in a solvent such as for example methylene chloride, by pyridine hydrobromide or hydrochloride or also by hydrobromic or hydrochloric acid in water or acetic acid under reflux.

25 The optional conversion of a haloalkyl radical into an alkylene radical of the products described above can be, if desired, carried out in the usual conditions known to a man skilled in the art, notably by saponification and dehalogenation for example in the presence of aqueous soda in an  
30 alcohol such as for example methanol.

The optional substitution reaction of a halogen atom by an amino radical of the products described above can be, if desired, carried out in the usual conditions known to a man skilled in the art, notably by treatment of the halogen  
35 compound with an amine derivative such as for example dimethylamine at ambient temperature in a solvent such as an alcohol such as for example ethanol or methanol.

The substitution reaction of a hydroxy radical by a

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halogen atom can be carried out in the usual conditions known to a man skilled in the art such as notably by chlorination with thionyl chloride.

The chlorinated derivative can be in its turn optionally substituted by an amine derivative such as for example dimethylamine.

The reduction reaction of an esterified carboxy radical into a hydroxyalkyl radical can be carried out in the usual conditions known to a man skilled in the art, such as notably by the action of lithium-aluminium hydride, diisobutyl-aluminium hydride or also other reducing agents known to a man skilled in the art.

The oxidation reaction of a hydroxyalkyl radical into an esterified carboxy radical can be carried out in the usual conditions known to a man skilled in the art, such as notably by an oxidizing mixture such as BOWERS reagent, followed by an esterification, for example with diazomethane.

The oxidation reaction of the hydroxymethyl radical into a formyl radical can be carried out in the usual conditions known to a man skilled in the art, such as notably by the action of activated manganese dioxide in methylene chloride.

The optional optically active forms of the products of formula ( $I_B$ ) can be prepared by resolution of the racemics according to the usual methods known to a man skilled in the art. The salts formed with optically active bases can for example be used.

The compounds of formula ( $I_B$ ) as defined above as well as their addition salts with acids have useful pharmacological properties.

The products are endowed with antagonistic properties for the angiotensin II receptor and are thus notably inhibitors of the effects of angiotensin II, in particular of the vasoconstricting effect and also of the trophic effect at the level of the myocytes.

These properties justify their use in therapeutics and a subject of the invention is also, as medicaments, the products as defined by formula ( $I_B$ ) above, the said products of formula ( $I_B$ ) being in all the possible racemic or optically active



isomer forms, as well as the addition salts with pharmaceutically acceptable mineral or organic acids and mineral or organic bases of the said products of formula (I<sub>B</sub>).

A subject of the invention is in particular, as  
5 medicaments, the products of formula (I<sub>B</sub>) as defined above in which R represents a butyl or 1-butenyl radical and R<sub>1B</sub> represents a hydrogen atom, and quite particularly the products of formula (I<sub>B</sub>) as defined above in which R represents a butyl radical and R<sub>1B</sub>, R<sub>2B</sub> and R<sub>5B</sub> are identical  
10 and each represents a hydrogen atom and R<sub>3B</sub> represents a hydrogen atom, a carboxy radical free or esterified by an alkyl radical containing at most 4 carbon atoms; a formyl radical; an alkyl or alkenyl radical containing at most 4 carbon atoms; an alkyl radical substituted by one or more  
15 radicals chosen from halogen atoms, hydroxyl radicals, acyloxy radicals, amino radicals optionally substituted by one or two alkyl radicals containing at most 4 carbon atoms and free, salified or esterified carboxy radicals, R<sub>4B</sub> represents a free, salified or esterified carboxy radical, an optionally  
20 salified cyano or tetrazolyl radical, as well as the addition salts with pharmaceutically acceptable mineral or organic acids and mineral or organic bases of the said products of formula (I<sub>B</sub>).

A more particular subject of the invention is, as  
25 medicaments, the following products of formula (I<sub>B</sub>):  
Methyl 4'-[(2-butyl-1H-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate,  
4'-[(2-butyl-1H-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,  
30 2-butyl-1-[[2'-carboxy biphenyl-4-yl]-methyl]-1H-benzimidazole-7-carboxylic acid,  
4'-[[2-butyl-7-(2-hydroxy ethyl)-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid,  
4'-[(2-butyl-7-formyl-1H-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,  
35 2-butyl-1-[[2'-(1H-tetrazol-5-yl)-(1,1'-biphenyl)-4-yl]-methyl]-1H-benzimidazole-7-carboxylic acid,  
as well as their addition salts with pharmaceutically



acceptable mineral or organic acids and mineral or organic bases. The medicaments which are a subject of the invention can be used in the treatment of arterial hypertension, cardiac insufficiencies, renal insufficiencies and in the prevention  
5 of post-angioplastic recurrences of stenosis.

They can also be used in the treatment of some gastrointestinal and gynaecological disorders and in particular for their relaxing effect at the level of the uterus.

The invention extends to pharmaceutical compositions  
10 containing as active ingredient at least one of the medicaments as defined above.

These pharmaceutical compositions can be administered by buccal or rectal route, by parenteral route or by local route as a topical application on the skin and mucous membranes.

15 These compositions can be solid or liquid and can be presented in all the pharmaceutical forms currently used in human medicine such as, for example, plain or sugar-coated tablets, capsules, granules, suppositories, injectable preparations, ointments, creams, gels and aerosol  
20 preparations; they are prepared according to the usual methods. The active ingredient can be incorporated with the excipients usually employed in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous  
25 vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agent, and preservatives.

The usual dosage, variable according to the product used, the patient treated and the affection in question, can be, for  
30 example, 1 to 100 mg per day for an adult, by oral route.

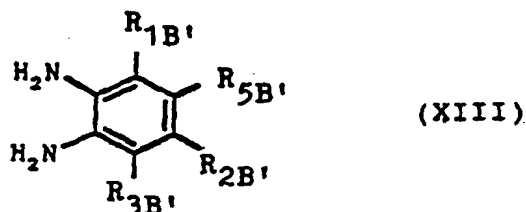
The starting compounds of formulae (II), (III), (IV<sub>B</sub>), (V<sub>B</sub>), (VI<sub>B</sub>) and (VI<sub>B</sub>') are commercially available or can be prepared according to the usual methods known to a man skilled in the art.

35 The preparation of some of the compounds of formula (IV<sub>B</sub>) is described in: J. Amer. Chem. Soc. (1937) 59, 178.

The other products of formula (IV<sub>B</sub>) can be prepared by the action of a compound of formula (III) as defined above



with a product of formula (XIII):



10

in which  $R_{1B'}$ ,  $R_{2B'}$ ,  $R_{3B'}$ , and  $R_{5B'}$  have the meaning indicated above.

The operating conditions are the same as those indicated above for the action of the products of formula (III) on the 15 products of formula (VIII<sub>g</sub>).

Some of the compounds of formula (XIII) are commercially available, such as for example methyl 3,4-diaminobenzoate, marketed for example by LANCASTER.

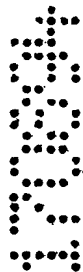
An example of the preparation of these compounds of 20 formula (XIII) is given in:

Journal of the Chemical Society, Chemical Communications, (1957) 2197-2201.

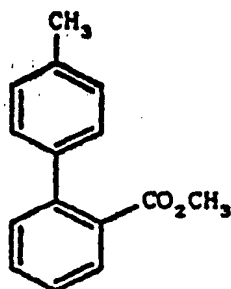
Among the compounds of formulae (II) and (III) there are found for example ethyl pentanimidoate which can be prepared, 25 for example, by the action of gaseous hydrochloric acid in ethanol on valeronitrile, marketed, for example, by LONZA.

An example of the preparation of these compounds of formula (III) is given in J. Amer. Chem. Soc. (1942), 64, 1827.

30 A preparation process for the products of formula (V<sub>g</sub>) as defined above can consist of subjecting methyl iodo-benzoate marketed for example by JANSSEN, to the action of iodotoluene, marketed for example by FLUKA, the reaction is carried out for example in the presence of powdered copper at 35 a temperature of 100°C to 300°C, in order to obtain a product of formula (V<sub>g</sub>):



5

(V<sub>B1</sub>)

10 the esterified carboxy radical of which can, if desired, be liberated from the alkyl radical by standard methods known to a man skilled in the art or as indicated above, for example acid or alkaline hydrolysis, which can be subjected to a bromination reaction on the methyl radical by standard methods  
15 known to a man skilled in the art, for example by the action of N-bromosuccinimide in carbon tetrachloride.

The preparation of some of the compounds of formula (V<sub>B</sub>) or (V<sub>B1</sub>) or also some of the conversions of the R<sub>4B</sub> radical of the products of formula (IX<sub>B</sub>) can be found, for example, in  
20 the Patent US 4,880,804 or EP 0,253,310.

The compound of formula (VI<sub>B</sub>) can be for example orthonitroaniline, in the form of the product marketed for example by UCB.

The products of formula (VI<sub>B</sub>) can also be prepared, for  
25 example, by the process described in:  
Canadian journal of chemistry, (1977), 55 (10), pp 1653-1657.

The products of formula (VI<sub>B1</sub>) which are aniline derivatives are commercially available such as for example 2,4-dimethoxy aniline from ALDRICH or can be prepared as well  
30 as is indicated for example in the following references:

- BEILSTEIN volume XII, 3rd supplement p. 1662
- BEILSTEIN volume XIII, 3rd supplement p. 2128.

Finally a subject of the present invention is, as new industrial products and notably as intermediate products  
35 necessary for the preparation of products of formula (I<sub>B</sub>), the compounds of formulae (IV<sub>B</sub>), (VII<sub>B</sub>), (VIII<sub>B</sub>), (X<sub>B</sub>) and (X<sub>B1</sub>).

In addition to the products described in the examples

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which illustrate the invention without however limiting it, the following products constitute products which can be obtained within the scope of the present invention: these products of formula (I<sub>A</sub>) are such that R represents a butyl radical, R<sub>4A</sub> represents a carboxy radical and R<sub>1A</sub>, R<sub>2A</sub>, R<sub>3A</sub> and R<sub>5A</sub> have the meanings indicated in the table below:



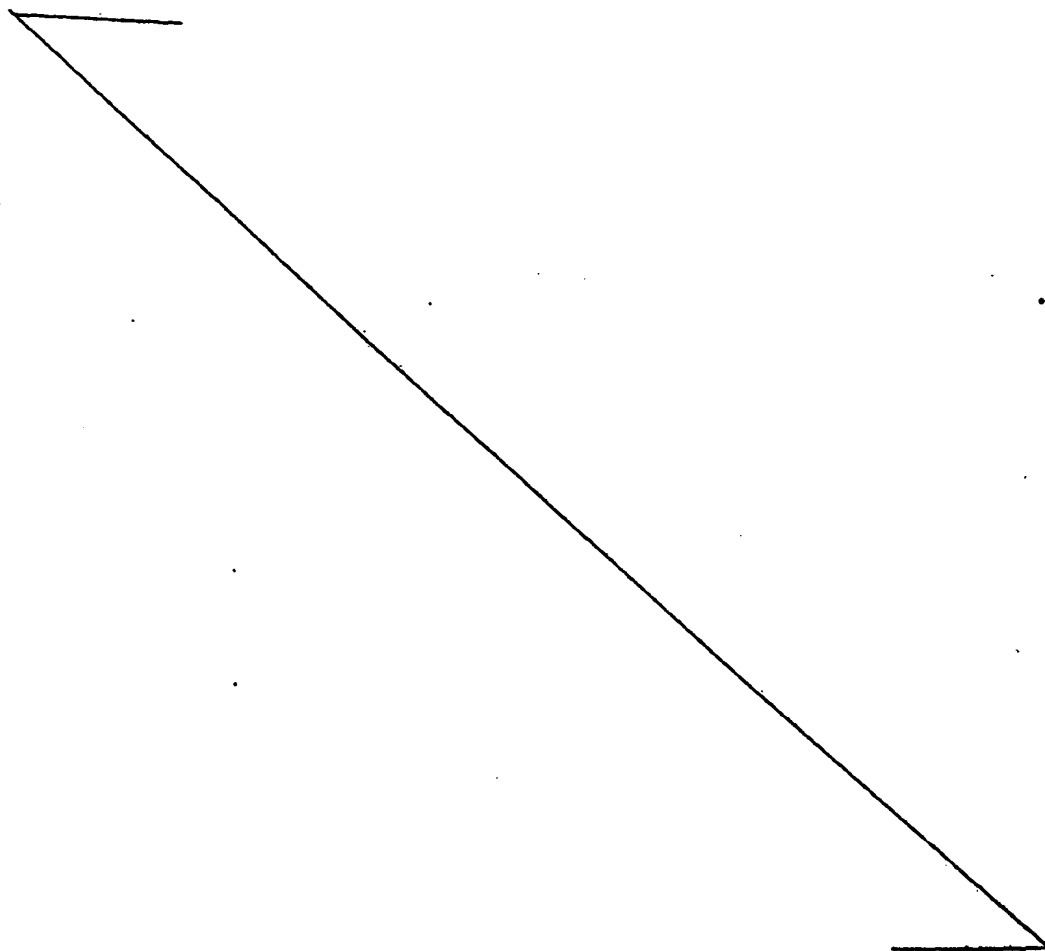
	R <sub>1B</sub>	R <sub>2B</sub>	R <sub>5B</sub>	R <sub>3B</sub>
5	H	H	H	OH
	H	H	H	COOMe
	H	H	H	CH <sub>3</sub>
	H	H	H	Cl
	H	CH <sub>2</sub> OH	H	OH
10	H	CH <sub>2</sub> OH	H	COOMe
	H	CH <sub>2</sub> OH	H	COOH
	H	CH <sub>2</sub> OH	H	CH <sub>3</sub>
	H	CH <sub>2</sub> OH	H	Cl
	H	CH <sub>2</sub> OH	H	CH <sub>2</sub> OH
15	H	CH <sub>2</sub> OH	H	CH <sub>2</sub> Cl
	H	CH <sub>2</sub> OH	H	CH <sub>2</sub> -CH <sub>2</sub> -OH
	H	CH <sub>2</sub> OH	H	CH <sub>2</sub> -CH <sub>2</sub> -Cl
	H	OCH <sub>3</sub>	H	OH
	H	OCH <sub>3</sub>	H	COOMe
20	H	OCH <sub>3</sub>	H	COOH
	H	OCH <sub>3</sub>	H	CH <sub>3</sub>
	H	OCH <sub>3</sub>	H	Cl
	H	OCH <sub>3</sub>	H	CH <sub>2</sub> OH
	H	OCH <sub>3</sub>	H	CH <sub>2</sub> Cl
25	H	OCH <sub>3</sub>	H	CH <sub>2</sub> -CH <sub>2</sub> -OH
	H	OCH <sub>3</sub>	H	CH <sub>2</sub> -CH <sub>2</sub> -Cl
	H	Cl	H	OH
	H	Cl	H	COOMe
	H	Cl	H	COOH
30	H	Cl	H	CH <sub>3</sub>
	H	Cl	H	Cl
	H	Cl	H	CH <sub>2</sub> OH
	H	Cl	H	CH <sub>2</sub> Cl
35	H	Cl	H	CH <sub>2</sub> -CH <sub>2</sub> -OH
	H	Cl	H	CH <sub>2</sub> -CH <sub>2</sub> -Cl



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30

5	R <sub>1B</sub>	R <sub>2B</sub>	R <sub>5B</sub>	R <sub>3B</sub>
	OH	H	H	OH
	OH	H	H	COOMe
10	OH	H	H	CH <sub>3</sub>
	OH	H	H	Cl
	OH	H	H	CH <sub>2</sub> OH
15	OH	H	H	CH <sub>2</sub> Cl
	OH	H	H	CH <sub>2</sub> -CH <sub>2</sub> -OH
	OH	H	H	CH <sub>2</sub> -CH <sub>2</sub> -Cl

20



The following examples illustrate the invention without however limiting it.

**EXAMPLE 1: Methyl 4'-((2-butyl-1H-benzimidazol-1-yl)-methyl)-biphenyl-2-carboxylate hydrochloride**

- 5 A solution of 2 g of 2-butyl-1H-benzimidazole (prepared according to W.O. Pool, HJ HARWOOD and AW RALSTON - J. Amer. Chem. Soc., (1937) 59, 178) in 3 cm<sup>3</sup> of dimethylformamide is added to a suspension of 650 mg of sodium methylate in 5 cm<sup>3</sup> of dimethylformamide cooled down to 0°C. The mixture is
- 10 agitated for 15 minutes while being allowed to return to ambient temperature. A solution of 3.6 g of methyl 4'-(bromomethyl)-biphenyl-2-carboxylate (obtained according to EP 0,253,310) in 5 cm<sup>3</sup> of dimethylformamide is added over 15 minutes.
- 15 Agitation is carried out for 4 hours at 40°C, the dimethylformamide is evaporated off and 50 cm<sup>3</sup> of an aqueous solution of sodium bicarbonate is added. After extraction three times with 100 cm<sup>3</sup> of ethyl acetate, the extracts are washed with water, dried, filtered and evaporated to dryness.
- 20 The residue (4.6 g) is chromatographed on silica (eluant: ethyl acetate - cyclohexane (1-1)). 1.8 g of desired product is obtained in the form of a base.

**Salification:**

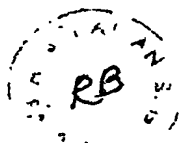
- A solution of hydrochloric ethyl acetate is added to a
- 25 solution of 500 mg of the base obtained above in isopropanol until an acid pH is obtained. The ethyl acetate is evaporated off, the product is crystallized from isopropanol, separated, washed with isopropanol, and dried under reduced pressure at 100°C. 350 mg of hydrochloride is obtained, M.p. = 155°C,
- 30 which is recrystallized twice from isopropanol. In this way 230 mg of the desired product is obtained in the form of the hydrochloride, M.p. = 155-160°C.

Analysis for C<sub>26</sub>H<sub>27</sub>N<sub>2</sub>O<sub>2</sub>Cl = 435.01

	C	H	Cl	N
35 % calculated	71.79	6.25	8.15	6.44
% found	72.00	6.2	8.3	6.3

IR Spectrum (CHCl<sub>3</sub>)

Absorption complex 2800  $\longrightarrow$  2000 cm<sup>-1</sup> (of the type:  $\geq N^{\oplus} - H$ )



$\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}-\text{OCH}_3 \end{array}$	1723 $\text{cm}^{-1}$
	1438 $\text{cm}^{-1}$
C=C	1620 $\text{cm}^{-1}$
C=N	1599 $\text{cm}^{-1}$
5 Aromatic	1558 $\text{cm}^{-1}$
	1510 $\text{cm}^{-1}$
	1488 $\text{cm}^{-1}$

**EXAMPLE 2: 4'-[(2-butyl-1H-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid**

- 10 0.8  $\text{cm}^3$  of 2N soda is added to a solution of 500 mg of the ester obtained in Example 1 in the form of a base in 8  $\text{cm}^3$  of methanol. Agitation is carried out for 4 hours under reflux. The methanol is evaporated off, the resultant mixture is cooled down to +10°C and acidified to a pH of 5-6 with 2N
- 15 hydrochloric acid, then agitated for 30 minutes at +10°C, separated, washed with water, dried at 80°C under reduced pressure. 400 mg of product is obtained, M.p. = 190°C, which is recrystallized twice from isopropanol in order to obtain 125 mg of the desired product. M.p. = 234°C.

20 Analysis for  $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_2 = 384.48$

	C	H	N
% calculated	78.10	6.29	7.28
% found	78.00	6.3	7.2

IR Spectrum (Nujol)

25 C=O	1682 $\text{cm}^{-1}$
Aromatic +	1615 $\text{cm}^{-1}$
heteroaromatic	1597 $\text{cm}^{-1}$
	1518 $\text{cm}^{-1}$

**PREPARATION 1: Methyl 4'-[N-[2-(methoxycarbonyl)-6-nitro-**

30 phenyl]-N-(pentanoyl)-aminomethyl]-biphenyl-2-carboxylate

**STAGE A: 2-amino-3-nitro benzoic acid**

**a) acetylation:**

- 0.65  $\text{cm}^3$  of concentrated sulphuric acid is added to a suspension cooled down to +10°C of 12 g of 2-amino-3-nitro
- 35 toluene and 14.4  $\text{cm}^3$  of acetic anhydride and the mixture is agitated for one hour at ambient temperature. 50  $\text{cm}^3$  of water is added, followed by agitation for 15 minutes, separating, washing with water then with ether, and drying at 100°C under



95  
23

reduced pressure. 13.6 g of desired product is obtained.

M.p. = 156°C.

b) oxidation:

13.4 g of the compound obtained above is added to a  
5 suspension of 29.48 g of potassium permanganate and 21.44 g of  
magnesium sulphate in 1470 cm<sup>3</sup> of water. The mixture is  
agitated for 3 hours at 100°C, allowed to return to ambient  
temperature, then cooled down to 0°C +5°C. The insoluble part  
is filtered off, 10 cm<sup>3</sup> of concentrated hydrochloric acid (pH  
10 2-3) is added to the filtrate which has been cooled down to  
0°C +5°C. Extraction is carried out 4 times with 500 cm<sup>3</sup> of  
ethyl acetate, the extracts are washed with water, dried,  
filtered and evaporated under reduced pressure. 16.1 g of  
product is obtained which is crystallized from ethyl ether in  
15 order to collect 12.1 g of the desired product. M.p. = 192°C.

c) hydrolysis:

12 g of the previously obtained product is agitated for 4  
hours at 120°C with 75 cm<sup>3</sup> of water with 5% concentrated  
hydrochloric acid, the mixture is allowed to return to ambient  
20 temperature, cooled down to 0°C +5°C, agitated for one hour at  
this temperature, separated, washed with water then with  
ether, and dried at 100°C under reduced pressure. 8.8 g of  
the desired product is obtained. M.p. = 210°C.

STAGE B: Methyl 2-amino-3-nitro benzoate

25 A suspension of 1 g of the acid obtained in Stage A, 15  
cm<sup>3</sup> of methanol and 1.4 cm<sup>3</sup> of 95-97% sulphuric acid is  
agitated under reflux for 48 hours. The methanol is  
evaporated off, 100 cm<sup>3</sup> of water is added, alkalization is  
carried out by adding sodium bicarbonate, followed by  
30 extracting 3 times with 200 cm<sup>3</sup> of methylene chloride. The  
extracts are washed with water, dried, filtered and evaporated  
under reduced pressure. 1 g of expected product is obtained.  
M.p. = 96°C.

STAGE C: Methyl 3-nitro-2-pentanamido benzoate

35 850 mg of product obtained in Stage B above and 5 cm<sup>3</sup> of  
valeryl chloride are agitated under reflux for one hour.  
After evaporation to dryness the residue is taken up in 80 cm<sup>3</sup>  
of ethyl ether, treated with activated charcoal, filtered and



evaporated under reduced pressure. 1.3 g of product is obtained which is crystallized from a mixture of isopropyl ether and pentane, and 1 g of desired product is collected. M.p. = 58°C.

5 An analytical sample was prepared by dissolution in 20 cm<sup>3</sup> of isopropyl ether under reflux, filtration and concentration to 5 cm<sup>3</sup>. The medium is left at rest for 18 hours at ambient temperature, separated, and washed with isopropyl ether. 710 mg is obtained. M.p. = 60°C.

10 This 710 mg is dissolved in 25 cm<sup>3</sup> of hot isopropyl ether, treated with activated charcoal, filtered, and concentrated to 10 cm<sup>3</sup>. This medium is left at rest at ambient temperature for one hour, separated, and washed with isopropyl ether. 380 mg of the desired product is obtained.

15 M.p. = 60°C.

Analysis for C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub> = 280.27

	C	H	N
% calculated	55.71	5.75	10.00
% found	55.8	5.38	9.9

20 IR Spectrum (CHCl<sub>3</sub>)

NH complex	3400 cm <sup>-1</sup> (ep)
	3330 cm <sup>-1</sup> (max)
C=O complex	1730 cm <sup>-1</sup> (ep)
	1708 cm <sup>-1</sup> (max)

25 Aromatic

+

Amide II

NO<sub>2</sub>

1608 - 1588 - 1499 cm<sup>-1</sup>

1540 - 1360 cm<sup>-1</sup>

STAGE D: Methyl 4'-[N-[2-(methoxycarbonyl)-6-nitro phenyl]-N-

30 (pentanoyl)-aminomethyl]-biphenyl-2-carboxylate

170 mg of sodium hydride at 50% in oil is added to a solution of 1 g of the product obtained in Stage B above in 5 cm<sup>3</sup> of dimethylformamide. Agitation is carried out for 5 minutes after the release of hydrogen has finished then 1.09 g of methyl 4'-(bromomethyl)-biphenyl-2-carboxylate (preparation EP 0,253,310) is added and agitation is carried out for one hour at ambient temperature. The solvent is evaporated off and the residue is taken up 3 times in 250 cm<sup>3</sup> of ethyl



acetate then washed 3 times with 50 cm<sup>3</sup> of water, dried, filtered and evaporated under reduced pressure. 2 g of product is obtained which is chromatographed on silica (eluant: methylene chloride - methanol 99-1). 1.6 g of the 5 desired product is collected.

IR Spectrum (CHCl<sub>3</sub>)

C=O complex 1726 and 1670 cm<sup>-1</sup>  
 NO<sub>2</sub> 1538 and 1352 cm<sup>-1</sup>  
 Aromatics 1600 and 1576 cm<sup>-1</sup>

10 **EXAMPLE 3: Methyl 2-butyl-1-[2'-(methoxycarbonyl)-biphenyl-4-yl]-methyl]-1H-benzimidazole-7-carboxylate hydrochloride**

a) hydrogenation:

365 mg of palladium at 18% on activated charcoal is added to a solution of 730 mg of the compound obtained in Stage D of 15 preparation 1 in 15 cm<sup>3</sup> of tetrahydrofuran. Agitation is carried out for one hour 30 minutes under a hydrogen atmosphere (109 cm<sup>3</sup> of hydrogen is absorbed), the catalyst is filtered off, the residue is rinsed with methylene chloride and evaporated to dryness under reduced pressure, and 730 mg 20 of product is obtained.

b) cyclisation:

730 mg of the above product is dissolved in 5 cm<sup>3</sup> of ethyl acetate and 5 cm<sup>3</sup> of isopropanol and a large excess of a solution of hydrochloric acid in ethyl acetate is added. The 25 mixture is heated to 50°C for 5 minutes and left for 30 minutes at ambient temperature, the solvents are evaporated off and the residue is taken up 3 times in 3 cm<sup>3</sup> of ethyl acetate. After separating and washing with ether, 640 mg of the desired product is obtained. M.p. = 160°C.

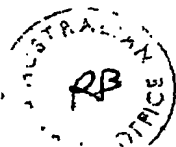
30 190 mg of the above product is recrystallized from isopropanol, and 163 mg of the expected product is obtained. M.p. = 160°C.

Analysis for C<sub>28</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>, HCl = 492.99

	C	H	Cl	N
35 % calculated	68.21	5.93	7.19	5.68
% found	67.8	5.8	7.3	5.5

IR Spectrum

Absorption complex type  $\equiv N^{\oplus}-H$  2380 cm<sup>-1</sup>





35  
36

C=O 1727 and 1721  $\text{cm}^{-1}$

**EXAMPLE 4: 2-butyl-1-[(2'-carboxy biphenyl-4-yl)-methyl]-1H-benzimidazole-7-carboxylic acid**

A solution of 440 mg of the product obtained in Example 3 with 10  $\text{cm}^3$  of ethanol, 1  $\text{cm}^3$  of water and 1  $\text{cm}^3$  of caustic soda lye is agitated for one hour under reflux. The ethanol is evaporated off, the residue is dissolved in water (10  $\text{cm}^3$ ) and the solution is acidified to pH 3-4 with acetic acid. After separating, 360 mg of product is obtained, M.p. = 160°C, then at 250°C, 450 mg of product obtained as above is recrystallized from 15  $\text{cm}^3$  of methanol, 5 drops of acetic acid and 5  $\text{cm}^3$  of water. 370 mg of product is obtained, M.p. = 255°C, which is dissolved in 20  $\text{cm}^3$  of methanol and 10  $\text{cm}^3$  of methylene chloride under reflux. The solution is filtered, the methylene chloride is evaporated off and one drop of acetic acid and 5  $\text{cm}^3$  of water are added. After one night at ambient temperature, separation is carried out and 330 mg of product is obtained. M.p. = 255°C.

Analysis for  $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_4 = 428.47$

20		C	H	N
	% calculated	72.88	5.65	6.54
	% found	73.0	5.6	6.5

IR Spectrum (nujol)

General absorption OH/NH region

25 C=O 1704  $\text{cm}^{-1}$

NMR Spectrum (DMSO)

	$\text{CH}_3$	0.88 (t)	
	$\text{CH}_2$	1.39 (m)	
	$\text{CH}_2$	1.76 (m)	
30	$\text{CH}_2\text{-C=}$	2.87 (m)	
	$\text{N-CH}_2\text{-}$	5.90 (s)	
	$\text{C}_6\text{H}_4$	6.88 (d,1)	7.23 (d,1)
	7 other H aromatics	7.20 to 7.90 (m)	
	mobile H's	approx. 12.95 (m)	

35 **PREPARATION 2: Methyl 4'-[N-[[2-nitro-6-[(pentanoyloxy)-methyl]-phenyl]-N-pentanoyl]-aminomethyl]-biphenyl-2-carboxylate**

**STAGE A: 2-amino-3-nitrobenzyl alcohol**



50 cm<sup>3</sup> of diisobutylaluminium hydride (in a 1.0 M solution in hexane) is added over one hour 30 minutes and at a temperature of between +7 and +8°C, to a solution of 3.54 g of the product obtained in Stage B of Preparation 1 in 90 cm<sup>3</sup> of 5 tetrahydrofuran. The resultant mixture is agitated for 30 minutes then, 40 cm<sup>3</sup> of tetrahydrofuran with 10% water is added over 15 minutes, with further agitation, then 10 cm<sup>3</sup> of water is added and agitation is continued for 30 minutes at ambient temperature, 350 cm<sup>3</sup> of methylene chloride with 10% 10 methanol is added, agitation is carried out for 15 minutes, followed by filtering and evaporating to dryness under reduced pressure. The residue obtained, 3.3 g, is crystal-lized from 10 cm<sup>3</sup> of isopropyl ether. 2.22 g of the desired product is obtained. M.p. = 110°C.

15 An analytical sample was obtained by recrystallizing 170 mg of the above product, hot and cold, from isopropyl ether. 80 mg of pure product is collected. M.p. = 112°C.  
Analysis for C<sub>7</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub> = 168.15

	C	H	N
20 % calculated	50.00	4.80	16.66
% found	49.8	4.8	16.5

IR Spectrum (CHCl<sub>3</sub>)

	OH	3604 cm <sup>-1</sup>
	=C-NH <sub>2</sub>	3498 - 3390 cm <sup>-1</sup>
25 NH <sub>2</sub> def	1624 cm <sup>-1</sup> (F)	
NO <sub>2</sub>	1520-1345 cm <sup>-1</sup> complex	
Aromatic	1580 cm <sup>-1</sup>	

STAGE B: 3-nitro-2-pentanamido benzyl pentanoate

1.5 g of the product obtained in Stage A and 15 cm<sup>3</sup> of 30 valeroyl chloride are agitated for 6 hours at ambient temperature. 80 cm<sup>3</sup> of essence G (B.p.40-70°C) is added, separation is carried out and 2.55 g of the desired product is obtained, M.p. = 82°C. After recrystallization of 118 mg of the above product from isopropyl ether, 72 mg of product is 35 collected, M.p. = 84°C.

Analysis for C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub> = 336.38

	C	H	N
% calculated	60.70	7.19	8.33



% found            60.7   7.3            8.4

IR Spectrum (CHCl<sub>3</sub>)

=C-NH            3426 cm<sup>-1</sup>

C=O            1734 and 1702 cm<sup>-1</sup>

5   Aromatics

NO<sub>2</sub> +            }   1610 - 1588 - 1538 - 1480 cm<sup>-1</sup>

Amide II        }

STAGE C: Methyl 4'-[N-[[2-nitro-6-[(pentanoyloxy)-methyl]-phenyl]-N-pentanoyl]-aminomethyl]-biphenyl-2-carboxylate   240

10 mg of sodium hydride at 50% in oil is added to a solution of 1.35 g of the product obtained in Stage B above in 13.5 cm<sup>3</sup> of dimethylformamide. The mixture is agitated for 15 minutes then 1.35 g of methyl 4'-(bromomethyl)-biphenyl-2-carboxylate (preparation according to EP 0,253,310); agitation is carried out  
15 for 30 minutes at ambient temperature, followed by extraction 3 times with 50 cm<sup>3</sup> of methylene chloride, and the extracts are washed with water, dried, filtered and evaporated to dryness under reduced pressure. The residue (2.7 g) is chromatographed on silica, (eluant: cyclohexane - ethyl acetate 8-2). 2.05 g of  
20 the desired product is obtained, used as it is (Rf 0.20 (cyclohexane - ethyl acetate 8-2)).

22

23



**EXAMPLE 5: 4'-[[2-butyl-7-(hydroxymethyl)-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid**

The operation is carried out as in Example 4, starting with 400 mg of Methyl 4'-[[2-butyl-7-[(pentanoyloxy)-methyl]-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate hydrochloride. 290 mg of desired product is obtained (M.p. = 250°C) which is recrystallized from aqueous ethanol in a slightly acetic medium, then from ethanol on its own, in order to collect 207 mg of the expected product, M.p. = 250°C.

Analysis for  $C_{26}H_{26}N_2O_3$  = 414.51

	C	H	N
% calculated	75.34	6.32	6.76
% found	75.2	6.3	6.8

IR Spectrum ( $CHCl_3$ )

Absorptions OH/NH approx.  $3480\text{ cm}^{-1}$

C=O  $1688\text{ cm}^{-1}$

Aromatic

+  $1598 - 1518\text{ cm}^{-1}$

Heterocycle

NMR Spectrum (DMSO) 300 MHz

$CH_3$  0.87 ppm (t)

$CH_2$  1.36 ppm (m)

$CH_2$  1.73 ppm (m)

$CH_2$  1.81 ppm (m)

$C_6H_4-CH_2-O-$  4.52 (s)

$C_6H_4$  6.91 (d)

7.28 (d)

the other aromatics approx. 7.08 (m) 2H - 7.32 1H -

approx. 7.54 (m) 2H - 7.70 (d) 1H - 5.50

**EXAMPLE 6: Methyl 4'-[[2-butyl-7-(hydroxymethyl)-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate**

A solution of 823 mg Methyl 4'-[[2-butyl-7-[(pentanoyloxy)-methyl]-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate hydrochloride in 8.2 cm<sup>3</sup> of ethanol and 1.6 cm<sup>3</sup> of 2N soda is agitated for 30 minutes. Then 10 cm<sup>3</sup> of water is added, followed by separating and drying, and 600 mg of the expected product is

obtained (M.p. = 138°C) which is recrystallized from ethyl acetate then isopropanol, M.p. = 140°C.

Analysis for  $C_{27}H_{28}N_2O_3$  = 428.51

	C	H	N
5 % calculated	75.67	6.59	6.54
% found	75.8	6.5	6.5

IR Spectrum ( $CHCl_3$ )

OH 3600  $cm^{-1}$

C=O 1722  $cm^{-1}$

10 **EXAMPLE 7: Methyl 4'-[[2-butyl-7-(chloromethyl)-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate hydro-chloride**

A solution of 1  $cm^3$  of thionyl chloride in 5  $cm^3$  of methylene chloride is added to a solution of 250 mg of the product obtained in Example 6 in 25  $cm^3$  of methylene chloride, and agitation is  
15 carried out for 15 minutes. After evaporation to dryness, the residue is crystallized from a mixture of ethyl acetate and ether. 250 mg of desired product is obtained. M.p. = 150°C.

Analysis for  $C_{27}H_{28}ClN_2O_2$  = 483.43

	C	H	Cl	N
20 % calculated	67.08	5.84	14.66	5.80
% found	67.0	5.9	14.4	5.9

IR Spectrum ( $CHCl_3$ )

C=O 1724  $cm^{-1}$

25 **EXAMPLE 8: 4'-[[2-butyl-7-(chloromethyl)-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid**

350 mg of the product obtained in Example 5 in 5  $cm^3$  of thionyl chloride is agitated for 2 hours at ambient temperature. After evaporation, about 5 g of ice then 20  $cm^3$  of water are added and agitation is carried out overnight at ambient  
30 temperature. The water is decanted, the residue is taken up in 30  $cm^3$  of methylene chloride, dried, filtered and evaporated to dryness under reduced pressure.

360 mg of the expected product is obtained in the form of an oil. CCM Rf = 0.40 (methylene chloride - methanol (9-1)).

35 **PREPARATION 3: Methyl 4'-[N-[2-nitro-6-[(2-pentanoyloxy)-ethyl]-phenyl]-N-pentanoyl]-aminomethyl]-biphenyl-2-**

43  
41

carboxylate

**STAGE A: 2-(2-pentanamido phenyl)-ethyl pentanoate**

The operation is carried out as in Stage B of Preparation 2 starting with 5 cm<sup>3</sup> of 2-amino phenethyl alcohol. 10.06 g of expected product is obtained, M.p. = 59°C. An analytical sample was prepared by 2 successive recrystallizations from essence G on 1.1 g of product, and 610 mg of purified product is obtained.

M.p. = 62°C.

10 Analysis for C<sub>18</sub>H<sub>27</sub>NO<sub>3</sub> = 305.42

	C	H	N
% calculated	70.79	8.91	4.59
% found	70.9	9.2	4.6

IR Spectrum (CHCl<sub>3</sub>)

15	 -C-NH	{ 3360 cm <sup>-1</sup> 3430 cm <sup>-1</sup>
	C=O	1684 cm <sup>-1</sup>
	Amide II	1530 cm <sup>-1</sup>
20	-O-C-    O	1720 cm <sup>-1</sup>

**STAGE B: 2-(3-nitro-2-pentanamido phenyl)-ethyl pentanoate**

7.1 cm<sup>3</sup> of acetic acid is added at a temperature of between 0° and +10°C to a solution of 9.1 g of the product obtained in Stage A above in 50 cm<sup>3</sup> of acetic anhydride.

25 Agitation is carried out for 2 hours between 0° and 10°C, 150 cm<sup>3</sup> of water is added, followed by separating and washing with water. 9.90 g of product is obtained which is chromatographed on silica (eluant: ethyl acetate - cyclohexane 30-70), and 5.89 g of desired product is obtained, M.p. = 117°C.

30 859 mg of the above product is recrystallized from isopropyl ether then from ether, and 494 mg of the expected product is collected. M.p. = 120°C.

Analysis for C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub> = 350.42

	C	H	N
35 % calculated	61.7	7.48	7.99
% found	61.5	7.5	7.9

IR Spectrum

| 3330 cm<sup>-1</sup>

RB

$\text{  }$ -C-NH	3420 $\text{cm}^{-1}$
C=O	1725 $\text{cm}^{-1}$
	1700 $\text{cm}^{-1}$
Aromatics	1605 $\text{cm}^{-1}$
5 + Amide II	1583 $\text{cm}^{-1}$
+ 1st $\text{NO}_2$ band	1535 $\text{cm}^{-1}$
	1478 $\text{cm}^{-1}$ (complex)
2nd $\text{NO}_2$ band	1348 $\text{cm}^{-1}$

10 STAGE C: Methyl 4'-[N-[[2-nitro-6-[(2-pentanoyloxy)-ethyl]-phenyl]-N-pentanoyl]-aminomethyl]-biphenyl-2-carboxylate

The operation is carried out as in Stage C of Preparation 2 starting with 3.5 g of the product obtained in Stage B above, using 480 mg of sodium hydride at 50% in oil and 3.05 g of methyl 4'-(bromomethyl)-biphenyl-2-carboxylate  
15 (preparation EP 0,253,310). After chromatography on silica (eluant: ethyl acetate - cyclohexane 3-7), 5.19 g of the desired product is obtained.

IR Spectrum ( $\text{CHCl}_3$ ) (PE 580).

$\text{>C=O}$	1728 $\text{cm}^{-1}$
20	1666 $\text{cm}^{-1}$

$\text{CH}_3$ of $\text{-C(=O)OCH}_3$	1438 $\text{cm}^{-1}$
---------------------------------------	-----------------------

$\text{NO}_2$	1534 $\text{cm}^{-1}$
---------------	-----------------------

25 EXAMPLE 9: Methyl 4'-[[2-butyl-7-(2-hydroxy ethyl)-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate

2.42 g of methyl 4'-[[2-butyl-7-[2-(pentanoyloxy)-ethyl]-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate with 20  $\text{cm}^3$



45  
A3

of methanol and 5.5 cm<sup>3</sup> of 1N soda is agitated for 30 minutes at ambient temperature. The methanol is evaporated off, followed by extraction with methylene chloride, the extracts are washed with water and evaporated to dryness under reduced pressure. The residue is crystallized from ethyl acetate, and 1.59 g of desired product is obtained. M.p. = 139°C. An analytical sample was prepared by recrystallization of 110 mg of the above product from ethyl acetate and 79 mg of product is collected. M.p. = 139°C.

10 Analysis for C<sub>23</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub> = 442.56

	C	H	N
% calculated	75.99	6.83	6.33
% found	75.8	6.8	6.2

IR Spectrum (CHCl<sub>3</sub>)

15 OH -	3615 cm <sup>-1</sup>
+ Associated	3550 cm <sup>-1</sup>
>C=O	1720 cm <sup>-1</sup>

<sup>10</sup>  
**EXAMPLE 12:** 4'-[[2-butyl-7-(2-hydroxy ethyl)-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid

20 The operation is carried out as in Example 4 starting with 400 mg of the product obtained in Example <sup>9</sup>11. 371 mg of expected product is obtained, M.p. = 174°C. The product is recrystallized twice from ethanol, and 96 mg of desired product is collected. M.p. = 175°C.

25 Analysis for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>, 1/2 C<sub>2</sub>H<sub>5</sub>OH = 451.574

	C	H	N
% calculated	74.48	6.92	6.20
% found	74.15	7.0	6.2

IR Spectrum

30 Absorption OH/NH region

>C=O	1680 cm <sup>-1</sup>
Conjugated system	1592 cm <sup>-1</sup>
+ Aromatic	1512 cm <sup>-1</sup>

NMR Spectrum (DMSO) 250 MHz

35 Presence of about 0.4 mol of ethanol

CH <sub>3</sub>	0.87 (t)
CH <sub>2</sub>	1.37 (m)
CH <sub>2</sub>	1.73 (m)





46  
44

CH <sub>2</sub>	2.80 (t)
C <sub>6</sub> H <sub>5</sub>	
CH <sub>2</sub>	2.88 (t)
CH <sub>2</sub>	3.62 (t)
5 OH	
N-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	5.71 (s)
C <sub>6</sub> H <sub>4</sub>	6.92 (d)
	7.29 (d)

the other aromatic H's 6.96 (d) 1H - 7.10 (t) 1H -  
10 7.34 (d) 1H - 7.40 to 7.60 3H  
7.70 (dd) 1H

mobile H 4.2 to 5.0

~~EXAMPLE 13: Methyl 4'-[[2-butyl-7-(2-chloro-ethyl)-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate hydro-~~  
15 ~~chloride~~

A mixture of 714 mg of the product obtained in Example 11 is agitated for 45 minutes at 80°C with 14 cm<sup>3</sup> of thionyl chloride. After evaporation of the thionyl chloride, the mixture is taken up 3 times with 20 cm<sup>3</sup> of methylene chloride and evaporated to dryness each time. The final dry extract is crystallized from ethyl acetate. 733 mg of desired product is obtained, M.p. = 151°C. A microanalytical sample was obtained by two successive recrystallizations from an ether - ethyl acetate mixture (1-1). The purified product is obtained.

25 M.p. = 160°C.

Analysis for C<sub>28</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub> = 497.47

	C	H	N	Cl
% calculated	67.60	6.08	5.63	14.25
% found	67.5	6.08	5.6	14.2

30 IR Spectrum CHCl<sub>3</sub>

Absorption type  $\geq N^+ - H$

O	1725 cm <sup>-1</sup>
-C-OCH <sub>3</sub>	1434 cm <sup>-1</sup>
Aromatic	1624 - 1600 - 1565 cm <sup>-1</sup>
35 Heteroaromatic	1512 - 1496 cm <sup>-1</sup>

~~EXAMPLE 14: 4'-[[2-butyl-7-(2-chloro-ethyl)-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid~~

~~500 mg of the product obtained in Example 13 is~~



**EXAMPLE 11: Methyl 4'-[[2-butyl-7-formyl-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate hydrochloride**

5 600 mg of the product obtained in Example 6 is dissolved in 60 cm<sup>3</sup> of methylene chloride and 1.2 g of activated manganese dioxide is added. The mixture is agitated for 24 hours at ambient temperature, filtered and evaporated to dryness under reduced pressure, and 600 mg of the expected

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product is obtained in the form of a base.

Preparation of the hydrochloride

600 mg of the product obtained above is dissolved in 3 cm<sup>3</sup> of ethyl acetate and a mixture of ethyl acetate and hydrochloric acid is added, in excess.

Separation is carried out, followed by washing with ether and drying at 80°C under reduced pressure.

610 mg of the expected hydrochloride is obtained. M.p. = 145°C.

IR Spectrum in CHCl<sub>3</sub>,

C=O 1723 - 1706 cm<sup>-1</sup>

Aromatic 1618 - 1599 - 1563 - 1520 cm<sup>-1</sup>

Heterocycles 1498 cm<sup>-1</sup>

EXAMPLE 12: 4'-[(2-butyl-7-formyl-1H-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid

600 mg of the product obtained in Example 11 is dissolved in 6 cm<sup>3</sup> of ethanol, 0.8 cm<sup>3</sup> of water and 0.8 cm<sup>3</sup> of caustic soda lye and agitation is carried out for 2 hour 30 minutes at 50°C. The mixture is cooled down, 30 cm<sup>3</sup> of water is added and acetic acid is added until a pH of 4-5 is obtained.

Agitation is carried out for 30 minutes at ambient temperature, followed by separating, washing with water and drying at 90°C under reduced pressure. 470 mg of product is obtained. M.p. = 225°C.

The product obtained above is dissolved in 30 cm<sup>3</sup> of methanol under reflux, followed by filtering, concentrating and leaving to crystallize at ambient temperature. The crystals are separated, washed with methanol and dried at 90°C under reduced pressure. 360 mg of the expected product is obtained. M.p. = 230°C.

Analysis for C<sub>26</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub> = 412.47

	C	H	N
% calculated	75.7	5.87	6.79
% found	75.5	5.8	6.7

IR Spectrum in Nujol

C=O 1690 cm<sup>-1</sup>

Aromatics 1600 - 1580 cm<sup>-1</sup>

Heterocycle 1516 cm<sup>-1</sup>



NMR Spectrum (DMSO) 300 MHz

CH <sub>3</sub>	0.88 (t)
CH <sub>2</sub>	1.38 (m)
CH <sub>2</sub>	1.75 (m)
CH <sub>2</sub>	2.88 (m)
C=O	
N-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	6.05 (sl)
C <sub>6</sub> H <sub>4</sub>	6.93 (d)
	7.25 (d)
	7.31 (d) 1H - 7.42 (m) 2H
the other aromatics	7.53 (td) 1H - 7.69 (d) 1H -
	7.83 (d) 1H - 8.0 (d) 1H
mobile protons	10.08 and 12.75

**EXAMPLE 13:** 4'-[[2-butyl-7-[(dimethylamino)-methyl]-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid dihydrochloride

360 mg of the product obtained in Example 8 is dissolved in 10 cm<sup>3</sup> of dimethylamine at 33% in ethanol and agitation is carried out for 19 hours at ambient temperature. The mixture is evaporated, extracted 3 times with 20 cm<sup>3</sup> of methylene chloride, washed twice with 15 cm<sup>3</sup> of salt water, dried, filtered and evaporated under reduced pressure. 300 mg of the expected product is obtained in the form of a base.

Preparation of the dihydrochloride

The operation is carried out as in Example 11, by dissolving 300 mg of the product obtained above in 5 cm<sup>3</sup> of isopropanol in the presence of an excess of ethyl acetate and hydrochloric acid.

110 mg of the expected product is obtained.

M.p. = 260°C.

Analysis for C<sub>28</sub>H<sub>31</sub>N<sub>3</sub>O<sub>2</sub>, 2HCl = 514.47

	C	H	Cl	N
% calculated	65.36	6.46	13.78	8.17
% found	65.3	6.5	13.8	8.0

IR Spectrum in Nujol

C=O	1770 - 1680 cm <sup>-1</sup>
Aromatics	1623 - 1597 cm <sup>-1</sup>
Heterocycles	1514 - 1495 cm <sup>-1</sup>



NMR Spectrum (DMSO) 300 MHz

	CH <sub>3</sub>	0.92 ppm (t)
	CH <sub>2</sub>	1.44 (m)
	CH <sub>2</sub>	1.83 (m)
5	CH <sub>2</sub>	3.24 (m)
	=C-CH <sub>2</sub> -N	4.38 (m)
	N-CH <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	5.98 (sl)
	C <sub>6</sub> H <sub>4</sub>	7.20 (d)
		7.34 (d)
10		7.56 (d) 1H - 7.88 (d) 1H
	the other aromatics	7.75 (d) 1H - 7.55 (m) 2H
		7.47 (t) 1H - approx. 7.37 masked 1H mobile protons
		11.39 and 12.78

**EXAMPLE 14: Methyl [2-butyl-1-[2'-(methoxycarbonyl)-biphenyl-4-yl]-methyl]-1H-benzimidazol-7-acetate hydrochloride**

a) Preparation of the [2-butyl-1-[2'-(methoxycarbonyl)-biphenyl-4-yl]-methyl]-1H-benzimidazol-7-acetic acid

1 g of the product obtained in Example 9 is introduced into 10 cm<sup>3</sup> of acetone and 1.5 cm<sup>3</sup> of BOWERS reagent. The mixture is agitated for one hour at ambient temperature, filtered, the filtrate is rinsed with methylene chloride, evaporated and the residue is taken up in 50 cm<sup>3</sup> of water and 50 cm<sup>3</sup> of methanol, brought to pH 12 with 1N soda, then acidified to pH 4-5 with acetic acid. After evaporation, extraction is carried out 3 times with 100 cm<sup>3</sup> of methylene chloride, and the extracts are washed twice with 40 cm<sup>3</sup> of water, dried, filtered and evaporated to dryness.

1.07 g of the expected product is obtained.

b) Preparation of methyl [2-butyl-1-[2-(methoxycarbonyl)-biphenyl-4-yl]-methyl]-1H-benzimidazol-7-acetate

The product obtained above is dissolved in 10 cm<sup>3</sup> of methylene chloride, then esterified with about 10 cm<sup>3</sup> of diazomethane in methylene chloride, evaporated to dryness and 968 mg of product is collected which is chromatographed on silica (eluant: ethyl acetate - flugene (7-3)).

745 mg of the expected product is obtained in the form of the base.

c) Preparation of the hydrochloride

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The operation is carried out as in Example 11, starting with 303 mg of the product obtained above in a mixture of ethyl acetate and hydrochloric acid. 280 mg of expected hydrochloride is obtained, M.p. = 128°C.

5 IR Spectrum in chloroform

Absorption type  $\geq N^{\oplus}-H$  approx. 2500  $cm^{-1}$

$>=O$  1725 - 1714  $cm^{-1}$

C-OMe 1438  $cm^{-1}$  (F)

O

10 Aromatics 1623 - 1599  $cm^{-1}$

Heteroaromatics 1565 - 1512 - 1500  $cm^{-1}$

**EXAMPLE 15:** 2-butyl-1-[(2'-carboxy-biphenyl-4-yl)-methyl]-1H-benzimidazol-7-acetic acid

15 745 mg of the product obtained in Example 14 is introduced at ambient temperature into 8  $cm^3$  of ethanol and 1.6  $cm^3$  of 32% soda and agitation is carried out for one hour under reflux of ethanol. The mixture is evaporated, the residue is taken up in 10  $cm^3$  of water acidified to pH 5 with acetic acid, separated, washed with water and dried under reduced pressure at 80°C. 516  
20 mg of expected product is obtained. M.p. = 161°C. Recrystallization is carried out from isopropanol then from methylethyl ketone. 184 mg of expected product is obtained. M.p. = 220°C.

Analysis for  $C_{27}H_{26}N_2O_4$  = 442.52

	C	H	N
% calculated	73.29	5.92	6.33
% found	73.3	5.9	6.3

IR Spectrum Nujol

OH/NH very associated general absorption

C=O 1712  $cm^{-1}$

NMR Spectrum (DMSO) 300 MHz

CH<sub>3</sub> 0.88 (t)

CH<sub>2</sub> 1.38 (m)

CH<sub>2</sub> 1.75 (m)

CH<sub>2</sub>-C $\equiv$  2.33 (t)

C<sub>6</sub>H<sub>5</sub>-CH<sub>2</sub>-C= 3.62 (s)

N-CH<sub>2</sub>-C<sub>6</sub>H<sub>5</sub> 5.65 (s)

$C_6H_4$	6.90 (d)
	7.29 (d)
	6.39 (d) 1H - 7.13 (t) 1H
the other aromatics	7.34 (d) 2H - 7.43 (dd) 2H
5	7.54 (m) 2H - 7.71 (dd) 1H
mobile H	12.75

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**EXAMPLE 16:** Methyl 4'-[[2-butyl-7-[(2-dimethylamino)-ethyl]-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate

1.05 g of methyl 4'-[[2-butyl-7-(2-chloro-ethyl)-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate

5 hydrochloride is introduced under agitation at ambient temperature into 25 cm<sup>3</sup> of dimethylamine at 33% in ethanol.

The mixture is maintained for 16 hours at 80°C, then evaporated under reduced pressure at 60°C, extracted 3 times with 60 cm<sup>3</sup> of methylene chloride, the extracts are washed 3  
10 times with 20 cm<sup>3</sup> of water, dried and evaporated to dryness.

After chromatography on silica, (eluant: methanol - methylene chloride (1-9)), 789 mg of the expected product is obtained. CCM: Rf 0.37 (eluant: methylene chloride - methanol (9-1)).

15 **EXAMPLE 17:** 4'-[[2-butyl-7-[2-(dimethylamino)-ethyl]-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid dihydrochloride

789 mg of the product obtained in Example 16 is introduced at ambient temperature into 15 cm<sup>3</sup> of ethanol and  
20 1.3 cm<sup>3</sup> of 32% soda.

The mixture is agitated for one hour at 85°C, evaporated, the residue is taken up in 10 cm<sup>3</sup> of water, acidified to pH 5 with acetic acid, and extracted 3 times with 60 cm<sup>3</sup> of methylene chloride; the extracts are washed twice with 10 cm<sup>3</sup>  
25 of water, dried, filtered and evaporated to dryness.

The resultant product is dissolved in 5 cm<sup>3</sup> of methylethylketone, 5 cm<sup>3</sup> of a mixture of ethyl acetate and hydrochloric acid is added and the whole is left to crystallize at ambient temperature, then the crystals are  
30 separated out, washed with methylethylketone and dried at 60°C under reduced pressure. After recrystallization from acetonitrile, 429 mg of the expected product is obtained. M.p. = 218°C.





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# Analysis for $C_{29}H_{33}N_3O_2 \cdot 2HCl$

	C	H	Cl	N
% calculated	65.9	6.67	13.42	7.95
% found	65.7	6.6	13.1	8.2

## 5 IR Spectrum Nujol

OH/NH very associated general absorption



	1708 $\text{cm}^{-1}$
	1690 $\text{cm}^{-1}$
Aromatic	1625 $\text{cm}^{-1}$
10 +	1598 $\text{cm}^{-1}$
Heteroaromatic	1569 $\text{cm}^{-1}$ 1510 $\text{cm}^{-1}$

## NMR Spectrum (DMSO) 250 MHz

	$\text{CH}_3$	0.91 (t)
	$\text{CH}_2$	1.42 (m)
15	$\text{CH}_2$	1.82 (m)
	$\text{CH}_2-\text{C}$	
	$\text{C}_6\text{H}_5-\text{CH}_2-\text{CH}_2-\text{N}$	3.09 (m) 2H
	and $=\text{C}-\text{CH}_2-\text{CH}_2$	3.26 (m) 4H
	$\text{N}-\text{CH}_2-\text{C}_6\text{H}_5$	6.04 (sl)
20	$\text{C}_6\text{H}_4$	7.23 (d) 2H
		7.34 (d) 2H
		7.80 (d) 1H - 7.74 (d) 1H
	the other aromatic H's	7.56 (m) 2H - 7.44 (m) 2H -
		7.30 (masked) 1H
25	the $\text{N}-\text{CH}_3$ 's	2.65 (sl)
	mobile H's	11.38

EXAMPLE 23: Methyl 2-butyl-1-[2'-cyano-(1,1'-biphenyl)-4-yl]-methyl]-1H-benzimidazol-7-carboxylate

STAGE A: Methyl 3-amino-2-pentanamido benzoate 560 mg of product obtained in Stage C of Preparation 1 is dissolved in 12  $\text{cm}^3$  of tetrahydrofuran, 280 mg of palladium at 18% on activated charcoal is added and the reaction medium is hydrogenated for 30 minutes (absorption 160  $\text{cm}^3$  of hydrogen). Agitation is carried out for a further 10 minutes, followed by filtering, the solvent is evaporated off under reduced pressure, the residue is taken up in isopropyl ether, separated and dried at 80°C under reduced pressure. 450 mg of crude product is recovered which is recrystallized from



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isopropyl ether. M.p. = 90°C.

Analysis for  $C_{13}H_{18}N_2O_3$ , 250.29

	C	H	N
% calculated	62.38	7.25	11.19
% found	62.4	7.4	11.1

IR Spectrum ( $CHCl_3$ )

-C-NH	3420 $cm^{-1}$	3340 $cm^{-1}$
C=O	1698 $cm^{-1}$ Max.	
	1680 $cm^{-1}$ Ep.	

- 10 Aromatic  
 NH<sub>2</sub> def.  
 Amide II
- 1620, 1601, 1580, 1514  $cm^{-1}$

STAGE B: Methyl 4'-[N-[[2-(methoxycarbonyl)-6-aminophenyl]-n-pentanoyl]-aminomethyl-biphenyl-2-carboxylate

- 15 52 mg of sodium hydride at 50% in oil is added to a solution of 250 mg of product obtained in Stage A above in 2  $cm^3$  of dimethylformamide, and the mixture is agitated for 15 minutes, then 300 mg of 4'-(bromomethyl)-biphenyl-2-nitrile is added and agitation is carried out for 15 minutes at ambient
- 20 temperature. The solvent is evaporated off, 60  $cm^3$  of water is added and extraction is carried out with methylene chloride; the extracts are washed with water, dried and evaporated to dryness under reduced pressure. 600 mg of crude expected product is collected which is chromatographed on
- 25 silica (eluant: flugene - ethyl acetate (7-3)) then crystallized from isopropyl ether then from ethyl ether.
- 125 mg of expected product is obtained. M.p. = 80°C then 145°C.

Analysis for  $C_{27}H_{27}N_3O_3$ , 441.51

	C	H	N
% calculated	73.45	6.16	9.52
% found	73.4	6.2	9.2

IR Spectrum ( $CHCl_3$ )

-C-NH <sub>2</sub>	3496 $cm^{-1}$	3395 $cm^{-1}$
35 -C=N	2226 $cm^{-1}$	
-C=O	1722 - 1656 $cm^{-1}$	
Aromatics	1613 $cm^{-1}$	1597 $cm^{-1}$
NH <sub>2</sub> def.	1588 $cm^{-1}$	1515 $cm^{-1}$



**STAGE C:** Methyl 2-butyl-1-[2'-cyano-(1,1'-biphenyl)-4-yl)-methyl]-1H-benzimidazol-7-carboxylate hydrochloride

730 mg of product obtained as in Stage B is dissolved in 10 cm<sup>3</sup> of a solution of hydrochloric acid in ethyl acetate and agitation is carried out for 10 minutes at 50°C. The solvent is evaporated off, the residue is taken up in a mixture of methylethylketone and ether, followed by separating and drying at 80°C under reduced pressure. 715 mg of crude product is obtained which is recrystallized from ethyl acetate then from a mixture of methylethylketone and ether. 270 mg of expected product is collected. M.p. = 140°C.

Analysis for C<sub>27</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>, HCl 459.96

	C	H	N	Cl
% calculated	70.50	5.70	9.14	7.71
% found	70.6	5.8	9.2	7.8

IR Spectrum (CHCl<sub>3</sub>)

-CO<sub>2</sub>CH<sub>3</sub> 1723 cm<sup>-1</sup> 1436 cm<sup>-1</sup>  
-C≡N 2226 cm<sup>-1</sup>

Complex absorptions max. to about 2450 cm<sup>-1</sup> of the type ON<sup>+</sup>-H

aromatics 1620 cm<sup>-1</sup> 1598 cm<sup>-1</sup>

Heteroaromatics 1564 cm<sup>-1</sup> 1496 cm<sup>-1</sup>

**EXAMPLE 19:** Methyl 2-butyl-1-[2'-(1H-tetrazol-5-yl)-(1,1'-biphenyl)-4-yl)-methyl]-1H-benzimidazol-7-carboxylate

a) 10 cm<sup>3</sup> of a saturated aqueous solution of sodium bicarbonate is added to a suspension containing 650 mg of the hydrochloride prepared in Example 18 in 50 cm<sup>3</sup> of water, the mixture is agitated for 10 minutes and extracted with methylene chloride with 2% methanol, the extracts are washed with water, dried, and the solvents are eliminated under reduced pressure. 600 mg of base is collected.

b) The 600 mg of above product is dissolved in 6 cm<sup>3</sup> of xylene and 511 mg of trimethyltin azide is added. After agitation for 23 hours at 115-120°C, a further 205 mg of azide is added and heating is continued for 24 hours. The xylene is evaporated off, 30 cm<sup>3</sup> of water is added, agitation is carried out for 15 minutes, 10 cm<sup>3</sup> of methanol is added, followed by extraction with methylene chloride; the extracts are dried and evaporated to dryness under reduced pressure.

1 g of crude product is obtained which is chromato-graphed on silica (eluant: methylene chloride - methanol (9-1)) then the residue is crystallized from ether. 470 mg of expected product is obtained. M.p. = 165°C.

5 **EXAMPLE 20: 2-butyl-1-((2'-(1H-tetrazol-5-yl)-(1,1'-biphenyl)-4-yl)-methyl)-1H-benzimidazol-7-carboxylic acid**

470 mg of product obtained in Example 19 in solution in 12 cm<sup>3</sup> of ethanol is agitated for 2 hours under reflux in the presence of 3 cm<sup>3</sup> of N soda, the ethanol is evaporated off, 10 cm<sup>3</sup> of water is added, then drop by drop 0.8 cm<sup>3</sup> of acetic acid is added. Agitation is carried out for 2 hours at ambient temperature, followed by separating, washing with water and drying at 80°C under reduced pressure. 420 mg of crude product is collected which is dissolved in 10 cm<sup>3</sup> of a methanol - methylethylketone mixture (1-1), the solution is filtered, concentrated to 5 cm<sup>3</sup>, one drop of acetic acid is added then 5 cm<sup>3</sup> of water is added, crystallization is started and left at +4°C for 16 hours; the crystals are separated, washed with water and dried at 90°C under reduced pressure. After recrystallization from ethyl acetate, 310 mg of expected product is obtained. M.p. = approx. 210-220°C.

Analysis for C<sub>26</sub>H<sub>24</sub>N<sub>6</sub>O<sub>2</sub>, 452.50

	C	H	N
% calculated	69.01	5.35	18.57
% found	68.7	5.3	18.3

IR Spectrum

Complex absorption OH/NH region

C=O 1700 cm<sup>-1</sup>

Aromatic 1609 cm<sup>-1</sup> 1598 cm<sup>-1</sup>

Heteroaromatic 1515 cm<sup>-1</sup> 1488 cm<sup>-1</sup>

**EXAMPLE 21: pharmaceutical composition**

Tablets were prepared corresponding to the following formula:

Product of Example 2 . . . . . 10 mg  
Excipient for a tablet completed at . . . . . 100 mg  
(detail of the excipient: lactose, talc, starch, magnesium stearate).

**EXAMPLE 22: pharmaceutical composition**

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Tablets were prepared corresponding to the following formula:

Product of Example 25 ..... 10 mg  
Excipient for a tablet completed at ..... 100 mg  
5 (detail of the excipient: lactose, talc, starch, magnesium stearate).

# PHARMACOLOGICAL RESULTS

## 1 - Test on the angiotensin II receptor

10 A fresh membrane preparation obtained from the liver of a rat is used. The tissue is ground up in a polytron in a Tris 50 mM buffer pH 7.4, the grinding is followed by 3 centrifugations at 30,000 g for 15 minutes, the deposits being taken up in between in the Tris buffer pH 7.4.

15 The last deposits are put in suspension in an incubation buffer (Tris 20 mM, NaCl 135 mM, KCl 10 mM, glucose 5 mM, MgCl<sub>2</sub> 10 mM phenylmethylsulphonyl fluoride 0.3 mM, bacitracin 0.1 mM, bis(trimethylsilyl) acetamide 0.2%).

The aliquoted fractions of 2 ml are divided into  
20 hemolysis tubes and I<sup>125</sup> angiotensin II (25,000 DPM per tube) and the product to be studied are added. (The product is first tested at 3 x 10<sup>-5</sup>M three times). When the tested product displaces by more than 50% the radioactivity linked specifically to the receptor, it is tested again according to  
25 a range of 7 concentrations in order to determine the concentration which inhibits by 50% the radioactivity linked specifically to the receptor. In this way the 50% inhibiting concentration is determined.

The non-specific bond is determined by addition of a  
30 reference product, namely the product of Example 94 of the European Patent 0,253,310, at 10<sup>-5</sup>M (in triplicate). The medium is incubated at 25°C for 150 minutes, put in a water bath at 0°C for 5 minutes, filtered under vacuum, rinsed with Tris buffer pH 7.4 and the radioactivity is counted in the  
35 presence of scintillating Triton.

The result is expressed directly as the 50% inhibiting concentration (IC<sub>50</sub>), that is as the concentration of studied product, expressed in nM, necessary to displace 50% of the



Results:

Product of Example	IC <sub>50</sub> in nanomoles
2	911
4	52
10	105
12	99
15	207
5	270

2 - Revealing the antagonistic activity of angiotensin II on the isolated portal vein

The portal vein of male Wistar rats (about 350 g) (IFFA Credo France) is removed after cervical dislocation and placed rapidly in a physiological solution (see below) at ambient temperature. A ring of about 1 mm diameter is mounted in a bath with an isolation mechanism, containing 20 ml of the following physiological solution (composition in mM: NaCl 118.3 - KCl 4.7 - MgSO<sub>4</sub> 1.2 - KH<sub>2</sub>PO<sub>4</sub> 1.2 - NaHCO<sub>3</sub> 25 - glucose 11.1 - CaCl<sub>2</sub> 2.5), the medium is maintained at 37°C and oxygenated with an O<sub>2</sub> (95%), CO<sub>2</sub> (5%) mixture. The initial pressure imposed is 1 g, the rings are left at rest for 60 to 90 minutes. In order to avoid spontaneous contractions, verapamil is added to the incubation bath (1.10<sup>-6</sup>M).

At the end of the rest period angiotensin II (Ciba hypertensin) 3.10<sup>-8</sup>M is added to the incubation bath and left in contact with the preparation for 1 minute. This operation is repeated every 30 minutes, the tissue being washed 3 or 4 times between two stimulations by angiotensin. The compound to be studied is introduced into the bath 15 minutes before a new stimulation by angiotensin. From increasing concentrations of the molecule being applied, an IC<sub>50</sub> (concentration which produces a 50% inhibition of the response to angiotensin) can be calculated, this being



expressed in nanomoles.

Results:

Product of Example	IC <sub>50</sub> in nanomoles
4	9.5
12	45
2	1000

3 - Test for antagonistic activity of angiotensin II in ademedullated rat

Male Sprague-Dawley rats (250 to 350 g) are anaesthetized by an intra-peritoneal injection of sodiumpentobarbital (50 mg/kg). The diastolic arterial pressure is recorded by means of a heparinized catheter (PE50) introduced into the left carotid of the animal, and connected to a pressure calculator (Gould, Pressure Processor) by means of a Gould pressure sensor.

A catheter is introduced into the right jugular vein of the animal in order to allow the injection of the molecules to be studied.

The animal is placed under assisted respiration. A bilateral section of the pneumogastric nerves is carried out. The rat is then demedullated.

After a sufficient period of stabilization, the study of the antagonism of the molecules vis- -vis angiotensin II (Hypertensin, CIBA) is approached in the following manner:

1 - Three consecutive injections of angiotensin II (0.75 micrograms/kg) spaced 15 minutes apart permits a reproducible and stable pressure response to be obtained.

2 - While keeping a time interval of 15 minutes for the administration of angiotensin II, the molecules (0.01 to 10 mg/kg) are injected 5 minutes before the angiotensin II. The pressure effects of angiotensin II in the presence of the antagonist are expressed as a percentage of the



pressure effects of angiotensin II administered on its own. The dose which inhibits the studied effect by 50% is thus determined ( $ID_{50}$ ).

Each animal is considered to be its own control.

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Results:

Product of Example	$IC_{50}$ in mg/kg
4	0.3
10	1.77
12	1.97

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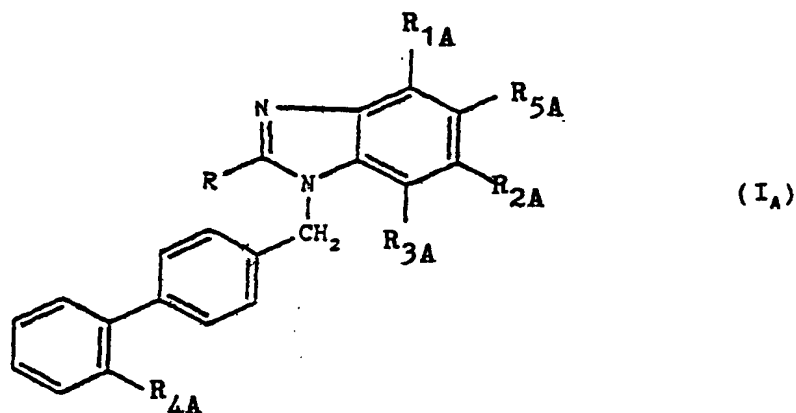
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The claims defining the invention are as follows:-

1) Products of formula (I<sub>A</sub>):



15 in which:

R represents a linear or branched alkyl or alkenyl radical containing 3 or 4 carbon atoms,

R<sub>1A</sub>, R<sub>2A</sub>, R<sub>3A</sub> and R<sub>5A</sub> are such that:

20 either R<sub>1A</sub>, R<sub>2A</sub>, R<sub>3A</sub> and R<sub>5A</sub> are identical and represent a hydrogen atom,

or R<sub>2A</sub> and R<sub>5A</sub> are such that one represents a hydrogen atom or a -CH<sub>2</sub>-O-R<sub>10</sub> radical, in which R<sub>10</sub> represents a hydrogen atom or or a linear or branched alkyl or alkenyl radical containing at most 5 carbon atoms, and the other represents a hydrogen atom, and R<sub>1A</sub> and R<sub>3A</sub> are such that one represents a hydrogen atom and the other is chosen from the radicals -OR<sub>6</sub>, -CO<sub>2</sub>R<sub>7</sub> and -R<sub>11</sub>, in which radicals:

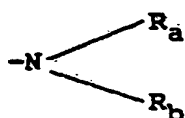
25 R<sub>6</sub> and R<sub>7</sub>, identical or different, represent a hydrogen atom or a linear or branched alkyl or alkenyl radical containing at most 5 carbon atoms,

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$R_{11}$  is chosen from the group formed by:

a) alkyl radicals having at most 4 carbon atoms, optionally substituted by one or more radicals chosen from:

- halogen atoms,
- the optionally acylated hydroxyl radical,
- linear or branched alkyloxy or alkenyloxy radicals having at most 5 carbon atoms,
- the free, esterified or salified carboxy radical,
- the radical:



in which  $R_a$  and  $R_b$ , identical or different, are chosen from hydrogen atoms, alkyl or alkenyl radicals having 1 to 4 carbon atoms optionally substituted by a halogen atom or a hydroxy radical,

b) linear or branched alkenyl radicals having 2 to 5 carbon atoms,

c) acyl radicals having 2 to 7 carbon atoms and the formyl radical,

$R_{4A}$  represents a free, esterified or salified carboxy radical, a cyano radical, or a tetrazolyl radical, optionally salified,

with the following provisos:

- (1) that when R is butyl and  $R_{4A}$  is  $-\text{CO}_2\text{H}$  or 2-tetrazolyl then  $R_{3A}$  is other than hydrogen; and
- (2) when  $R_{4A}$  is t-butylexycarbonyl or 1-(triphenylmethyl)-tetrazolyl,

then

- (a)  $R_{1A}$ ,  $R_{2A}$ ,  $R_{3A}$ , and  $R_{5A}$  may not all be hydrogen
- (b) if three of  $R_{1A}$ ,  $R_{2A}$ ,  $R_{3A}$ ,  $R_{5A}$  are hydrogen the other may not be alkyl optionally substituted by hydroxy, alkoxy, amino, alkylamino and dialkylamino; alkoxy; or acyl
- (c) if two of  $R_{1A}$ ,  $R_{2A}$ ,  $R_{3A}$ ,  $R_{5A}$  are hydrogen then the other two may not simultaneously be alkyl optionally substituted by hydroxy, alkoxy, amino, alkylamino and dialkylamino; alkoxy; or acyl,



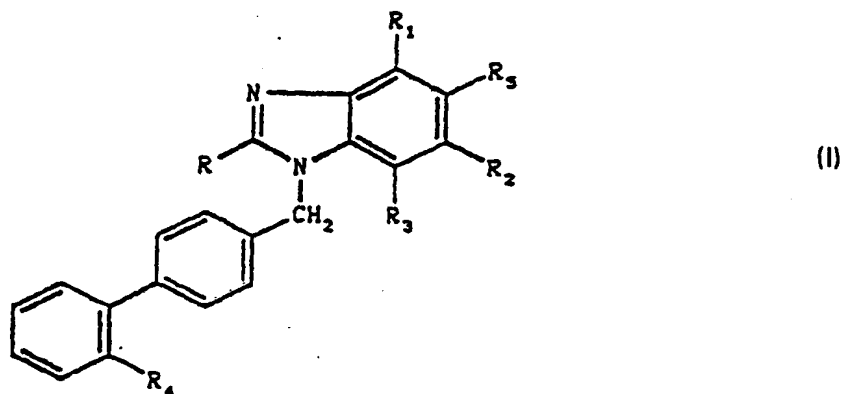
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and (3) when R is butyl and  $R_{1A}$ ,  $R_{2A}$ ,  $R_{3A}$ ,  $R_{5A}$  are all hydrogen, then,  $R_{4A}$  is not -  $\text{CO}_2\text{CH}_2\text{CH}_3$ .

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2) Products of formulae (I<sub>A</sub>), as defined in claim 1 corresponding to formula (I):



in which:

15 R represents a linear or branched alkyl or alkenyl radical containing 3 or 4 carbon atoms,

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>5</sub> are such that:

either R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>5</sub> are identical and represent a hydrogen atom,

or R<sub>2</sub> and R<sub>5</sub> are such that one represents a hydrogen atom or a -CH<sub>2</sub>-O-R<sub>10</sub> radical and the other represents a hydrogen atom, and R<sub>1</sub> and R<sub>3</sub> are such that: one represents a hydrogen atom and the other is chosen from the radicals -OR<sub>6</sub>, -CO<sub>2</sub>R<sub>7</sub> and -CH<sub>2</sub>-O-R<sub>8</sub>, which radicals R<sub>10</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub>, identical or different, represent a hydrogen atom or a linear or branched alkyl or alkenyl radical containing at most 5 carbon atoms,

25 R<sub>4</sub> represents a free, esterified or saltified carboxy radical, the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral or organic acids and mineral or organic bases of the said products of formula (I).



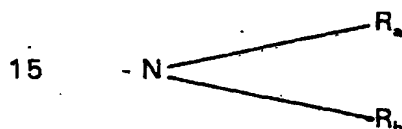
3) Products of formula (I<sub>A</sub>) as defined in claim 1, in which R represents a butyl radical, R<sub>1A</sub>, R<sub>2A</sub>, and R<sub>5A</sub> represent a hydrogen atom, and R<sub>3A</sub> is chosen from the radicals -OR<sub>6</sub>, -CO<sub>2</sub>R<sub>7</sub> and -R<sub>11</sub>, in which radicals:

5 R<sub>6</sub> and R<sub>7</sub>, identical or different, represent a hydrogen atom or a linear or branched alkyl or alkenyl radical containing at most 5 carbon atoms,

R<sub>11</sub> is chosen from the group formed by:

a) alkyl radicals having at most 4 carbon atoms, optionally substituted by one or more radicals chosen from:

- halogen atoms,
- 10 - the optionally acylated hydroxy radical,
- linear or branched alkyloxy or alkenyloxy radicals having at most 5 carbon atoms,
- the free, esterified or salified carboxy radical,
- the radical:



in which R<sub>a</sub> and R<sub>b</sub>, identical or different, are chosen from hydrogen atoms, alkyl or alkenyl radicals having 1 to 4 carbon atoms optionally substituted by a halogen atom or a hydroxy radical,

20

b) linear or branched alkenyl radicals having 2 to 5 carbon atoms,

c) acyl radicals having 2 to 7 carbon atoms and the formyl

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radical, the said products of formula (I<sub>A</sub>) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral or organic acids and mineral or organic bases of the said products of formula (I<sub>A</sub>).

- 5 4) Products of formula (I<sub>A</sub>) as defined in claim 1, 3 or 4, in which R represents a butyl radical and R<sub>1A</sub>, R<sub>2A</sub> and R<sub>3A</sub> represent a hydrogen atom, and R<sub>3A</sub> represents a carboxy radical, free or esterified by an alkyl radical containing at most 4 carbon atoms; a formyl radical; an alkenyl radical containing at most 4 carbon atoms; an alkyl radical containing at most 4 carbon atoms and being substituted by one or  
10 more radicals chosen from halogen atoms, acyloxy radicals, amino radicals optionally substituted by one or two alkyl radicals containing at most 4 carbon atoms and free, salified or esterified carboxy radicals, the said products of formula (I<sub>A</sub>) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral or organic acids and mineral or  
15 organic bases of the said products of formula (I<sub>A</sub>).

5) Methyl 4'-[(2-butyl-1H-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate, 2-butyl-1-[(2'-carboxy-biphenyl-4-yl)-methyl]-1H-benzimidazole-7-carboxylic acid, 4'-[(2-butyl-7-(2-hydroxy ethyl)-1H-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid,

20 4'-[(2-butyl-7-formyl-1H-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid, 2-butyl-1-[(2'-(1H-tetrazol-5-yl)-(1,1'-biphenyl)-4-yl)-methyl]-1H-benzimidazol-7-carboxylic acid, methyl 2-butyl-1-[2'-(methoxycarbonyl)-biphenyl-4-yl]-methyl]-1H-benzimidazol-7-carboxylate hydrochloride,

25 4'-[(2-butyl-7-(hydroxymethyl)-1H-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylic acid, methyl 4'-[(2-butyl-7-(hydroxymethyl)-1H-benzimidazol-1-yl)-methyl]-biphenyl-2-carboxylate, methyl 4'-[(2-butyl-7-(chloromethyl)-1H-benzimidazol-1-yl)-

- methyl]-biphenyl-2-carboxylate hydrochloride,  
 4'-[[2-butyl-7-(chloromethyl)-1H-benzimidazol-1-yl]-methyl]-  
 biphenyl-2-carboxylic acid,  
 methyl 4'-[[2-butyl-7-(2-hydroxy ethyl)-1H-benzimidazol-1-  
 5 yl]-methyl]-biphenyl-2-carboxylate,  
 methyl 4'-[[2-butyl-7-formyl-1H-benzimidazol-1-yl]-methyl]-  
 biphenyl-2-carboxylate hydrochloride,  
 4'-[[2-butyl-7-[(dimethylamino)-methyl]-1H-benzimidazol-1-  
 yl]-methyl]-biphenyl-2-carboxylic acid dihydrochloride,  
 10 methyl [[2-butyl-1-(2'-methoxycarbonyl)-biphenyl-4-yl]-  
 methyl]-1H-benzimidazol-7-acetate hydrochloride,  
 2-butyl-1-[(2'-carboxy-biphenyl-4-yl)-methyl]-1H-  
 benzimidazol-7-acetic acid,  
 methyl 4'-[[2-butyl-7-[(2-dimethylamino)-ethyl]-1H-  
 15 benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylate,  
 4'-[[2-butyl-7-[2-(dimethylamino)-ethyl]-1H-benzimidazol-1-  
 yl]-methyl]-biphenyl-2-carboxylic acid dihydrochloride,  
 methyl 2-butyl-1-[2'-cyano-(1,1'-biphenyl)-4-yl]-methyl]-1H-  
 benzimidazol-7-carboxylate,  
 20 methyl 2-butyl-1-[2'-(1H-tetrazol-5-yl)-(1,1'-biphenyl)-4-  
 yl]-methyl]-1H-benzimidazol-7-carboxylate,

being in all the possible racemic, enantiomeric and  
 diastereoisomeric isomer forms, as well as the salts,

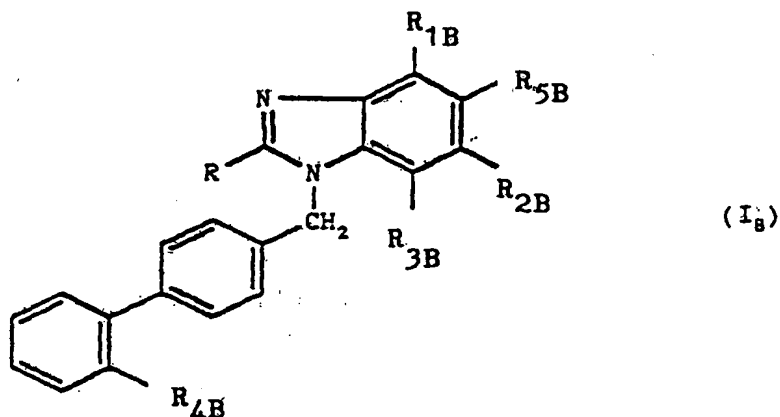
- 25 addition salts with mineral or organic acids and mineral or  
 organic bases thereof.

6 ) Methyl 4'-[[2-butyl-1H-benzimidazol-1-yl]-methyl]-  
 biphenyl-2-carboxylate hydrochloride.

7 ) Preparation process for products of formula (I<sub>B</sub>)

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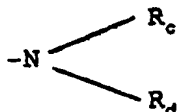


in which:

R represents a linear or branched alkyl or alkenyl radical containing 3 or 4 carbon atoms,

$R_{18}$ ,  $R_{28}$ ,  $R_{38}$  and  $R_{58}$  are such that:

- 5 either  $R_{18}$ ,  $R_{28}$ ,  $R_{38}$  and  $R_{58}$  are identical and represent a hydrogen atom,  
 or  $R_{28}$  and  $R_{58}$  are such that one represents a hydrogen atom and the other represents a hydrogen atom or a  $-\text{CH}_2-\text{O}-R_{10}$  radical, in which  $R_{10}$  represents a hydrogen atom or a linear or  
 10 branched alkyl or alkenyl radical containing at most 5 carbon atoms, or one of  $R_{28}$  and  $R_{58}$  represent the radical

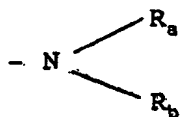


- 15 in which  $R_c$  and  $R_d$ , identical or different, represents the values defined hereafter for  $R_a$  and  $R_b$  and  $R_{18}$  and  $R_{38}$  are such that one represents a hydrogen atom and the other is chosen from the radicals  $-\text{OR}_6$ ,  $-\text{CO}_2R_7$  and  $-\text{R}_{11}$ , in which radicals:  
 $R_6$  and  $R_7$ , identical or different, represent a hydrogen atom  
 20 or a linear or branched alkyl or alkenyl radical containing at most 5 carbon atoms,

$R_{11}$  is chosen from the group formed by:

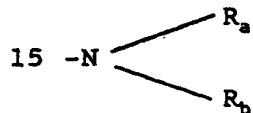
a) alkyl radicals having at most 4 carbon atoms, optionally substituted by one or more radicals chosen from:

- 25 - halogen atoms,  
 - the optionally acylated hydroxyl radical,  
 - linear or branched alkyloxy or alkenyloxy radical having at most 5 carbon atoms,  
 - aryl radicals optionally substituted by one or more  
 30 radicals chosen from halogen atoms, hydroxyl, trifluoromethyl, cyano, nitro, amino radicals, alkoxy radicals containing at most 4 carbon atoms, phenyl, benzyl radicals, free, salified or esterified carboxy radicals and tetrazolyl radicals,  
 35 - the free, esterified or salified carboxy radical,  
 - the radical:

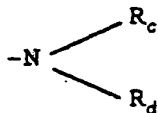




- in which  $R_a$  and  $R_b$ , identical or different, are chosen from hydrogen atoms, alkyl or alkenyl radicals having 1 to 4 carbon atoms and aryl radicals, all these radicals being optionally substituted by one or more radicals chosen from
- 5 halogen atoms, or the hydroxyl, trifluoromethyl, cyano, nitro or amino radical, alkoxy radicals containing at most 4 carbon atoms, phenyl or benzyl radicals, free, salified or esterified carboxy radicals and tetrazolyl radicals,
- b) linear or branched alkenyl radicals having 2 to 5 carbon
- 10 atoms,
- c) acyl radicals having 2 to 7 carbon atoms and the formyl radical,
- d) the radical:



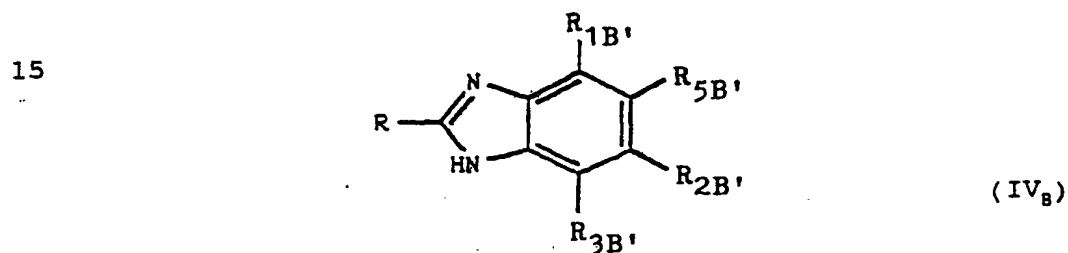
- in which  $R_a$  and  $R_b$  have the meaning indicated above, or one at most of  $R_{18}$ ,  $R_{28}$ ,  $R_{38}$  and  $R_{58}$  represents a hydrogen atom,
- 20 and the others are chosen from the radicals  $-\text{CH}_2-\text{O}-R_{10}$ ,  $-\text{OR}_6$ ,  $-\text{CO}_2R_7$ ,  $-\text{R}_{11}$  and the radical



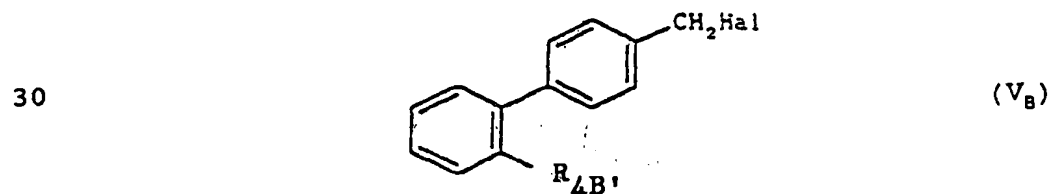
- 25 in which  $R_6$ ,  $R_7$ ,  $R_{10}$ ,  $R_{11}$ ,  $R_c$  and  $R_d$  have the values indicated above,
- $R_{48}$  represents a free, esterified or salified carboxy radical, or a tetrazolyl radical,
- or a  $-(\text{CH}_2)_m-\text{SO}_2-\text{X}-\text{R}_{12}$  radical in which  $m$  represents an integer
- 30 from 0 to 4 and
- either  $(\text{X}-\text{R}_{12})$  represents  $\text{NH}_2$
- or  $\text{X}$  represents a single bond, or the radicals  $-\text{NH}-$ ,  $-\text{NH}-\text{CO}-$ ,  $-\text{NH}-$  or  $-\text{NH}-\text{CO}-$  and  $\text{R}_{12}$  represents an alkyl, alkenyl or aryl radical, these radicals being optionally substituted,
- 35 the said products of formula  $(I_8)$  being in all the possible racemic, enantiomeric or diastereoisomeric isomer forms, as well as the addition salts with mineral or organic acids and mineral or organic bases of the said products of formula  $(I_8)$ .
- ~~2) Products of formula  $(I_8)$ , as defined in claim 1, in~~



~~substituted, all this radicals being optionally substituted~~  
 by one or more selected from the halogen atoms, the hydroxy  
 radical, alkyl, alkenyl and alkoxy radical containing at most  
 4 carbon atoms, trifluoromethyl, cyano, free, salified or  
 5 esterified carboxy or tetrazolyl radical, the said products  
 of formula (I<sub>B</sub>) being in all the possible racemic,  
 enantiomeric and diastereoisomeric isomer forms, as well as  
 the addition salts with mineral or organic acids and mineral  
~~or organic bases of the said products of formula (I<sub>B</sub>)~~  
 10 characterized in that:  
 either a product of formula (IV<sub>B</sub>):



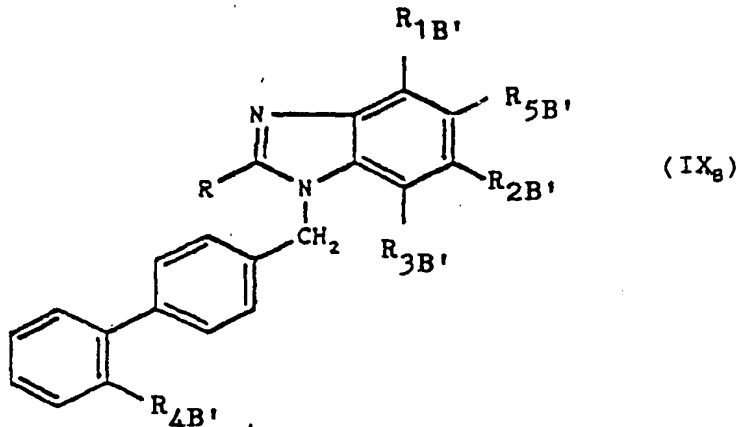
in which R has the meaning indicated above and R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>  
 and R<sub>5B'</sub> have the meanings indicated above for R<sub>1B</sub>, R<sub>2B</sub>, R<sub>3B</sub> and  
 R<sub>5B</sub> respectively in which the optional reactive functions are  
 25 if desired protected by protective groups, is reacted with a  
 compound of formula (V<sub>B</sub>):



in which Hal represents a halogen atom and R<sub>4B'</sub> has the meaning  
 35 indicated above for R<sub>4B</sub> in which the optional reactive  
 functions are, if desired, protected by protective groups, in  
 order to obtain a product of formula (IX<sub>B</sub>):

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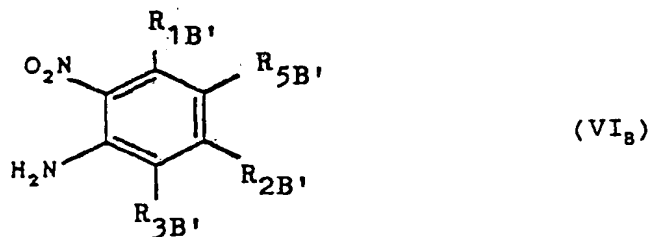
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in which R, R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, R<sub>5B'</sub>, and R<sub>4B'</sub> have the meanings indicated above,

or

a) a compound of formula (VI<sub>B</sub>):

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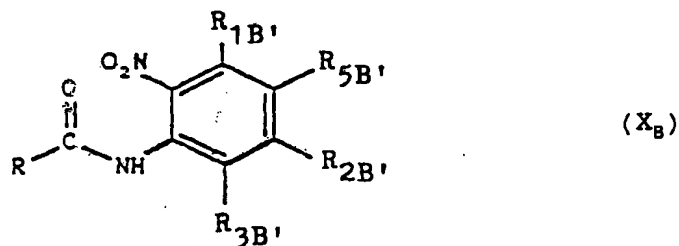
in which R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, and R<sub>5B'</sub> have the previous meanings, is reacted with the compound of formula (II):



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in which R<sub>9</sub> represents a hydroxy or alkyloxy radical or a halogen atom and R has the meaning indicated above, in order to obtain the product of formula (X<sub>B</sub>):

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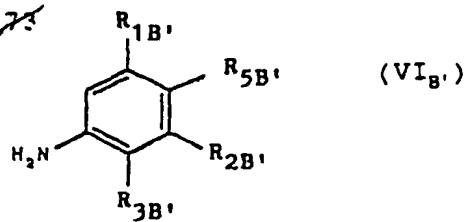


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in which R, R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, and R<sub>5B'</sub> have the previous meanings, b) a compound of formula (VI<sub>B</sub>):

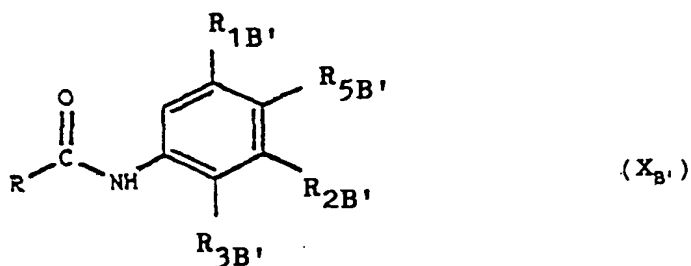
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5 in which R<sub>1B</sub>', R<sub>2B</sub>', R<sub>3B</sub>', and R<sub>5B</sub>' have the previous meanings,  
is reacted with the compound of formula (II) as defined above  
in order to obtain the product of formula (X<sub>B</sub>):

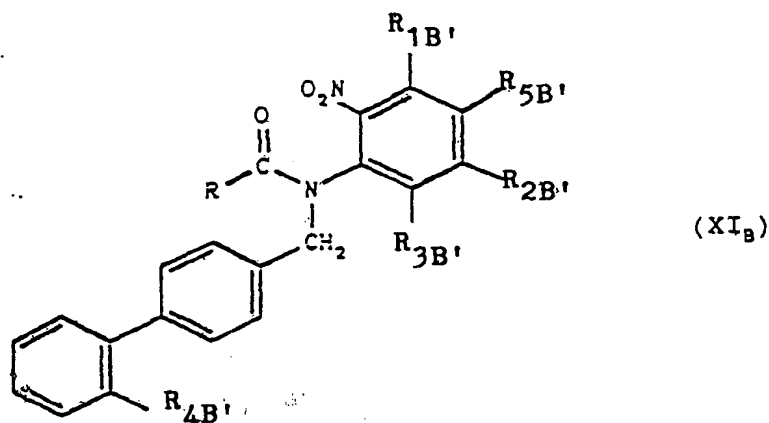
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in which R<sub>1B</sub>', R<sub>2B</sub>', R<sub>3B</sub>', R<sub>5B</sub>' and R have the meanings indicated  
previously,  
which is subjected to a nitration reaction in order to obtain  
20 the compound of formula (X<sub>B</sub>) as defined above,  
which product of formula (X<sub>B</sub>) is reacted with the compound of  
formula (V<sub>B</sub>) as defined above, in order to obtain a product of  
formula (XI<sub>B</sub>):

25



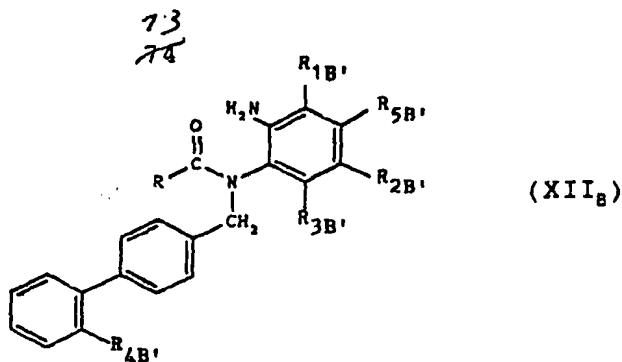
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35 in which R, R<sub>1B</sub>', R<sub>2B</sub>', R<sub>3B</sub>', R<sub>5B</sub>' and R<sub>4B</sub>' have the previous  
meanings, which is subjected to a selective reduction  
reaction of the nitro function, in order to obtain the  
product of formula (XII<sub>B</sub>):

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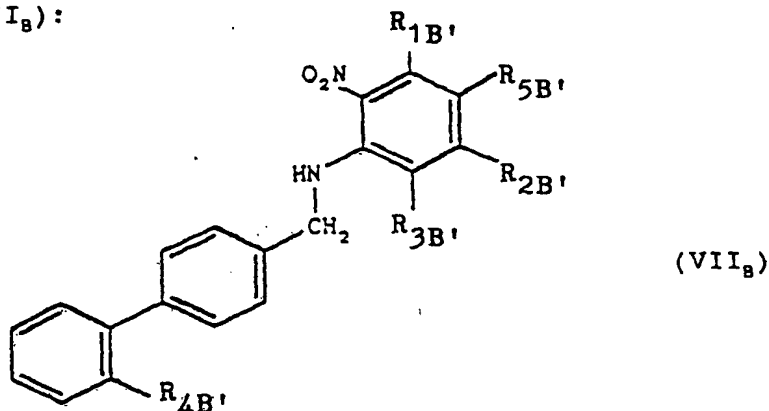
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in which R, R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, R<sub>5B'</sub>, and R<sub>4B'</sub> have the previous meanings, which is subjected to a cyclization reaction in order to obtain the products of formula (IX<sub>B</sub>) as defined above,

or the compound of formula (VI<sub>B</sub>) is reacted with the compound of formula (V<sub>B</sub>) as defined above, in order to obtain a product of formula (VII<sub>B</sub>):

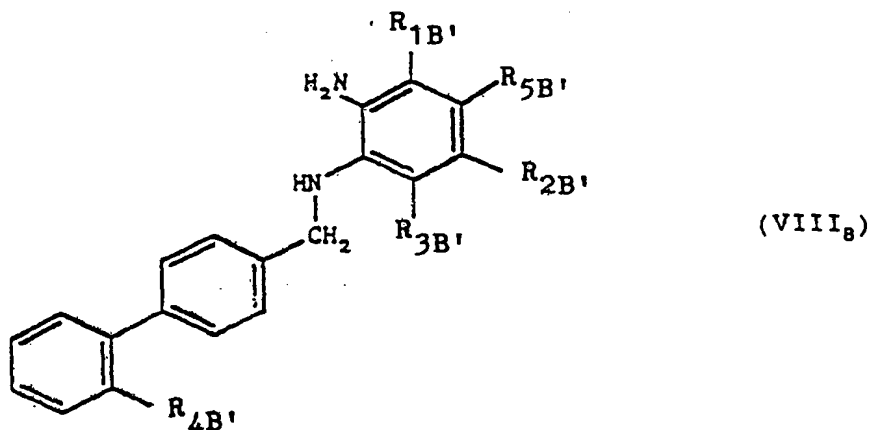
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25 in which R<sub>1B'</sub>, R<sub>2B'</sub>, R<sub>3B'</sub>, R<sub>5B'</sub>, and R<sub>4B'</sub> have the meanings indicated above, which is subjected to a reduction reaction of the nitro radical into an amino radical in order to obtain a product of formula (VIII<sub>B</sub>):

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in which  $R_{18}$ ,  $R_{28}$ ,  $R_{38}$ ,  $R_{58}$ , and  $R_{48}$ , have the meanings indicated above, which is reacted with the product of formula (III):



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in which X represents an oxygen atom or an NH radical,  $R_9$  and R have the meaning indicated above, in order to obtain after cyclization a product of formula (IX<sub>8</sub>) as defined above, which product of formula (IX<sub>8</sub>), if desired and if necessary,

10 is subjected to one or more of the following reactions, in any order:

- an elimination reaction of the protector groups which can be carried by the protected reactive functions,
  - a salification reaction by a mineral or organic acid or
  - 15 base in order to obtain the corresponding salt,
  - an esterification or salification reaction of the acid function,
  - an acid or alkaline hydrolysis reaction of the ester function into an acid function,
  - 20 - a conversion reaction of an alkyloxy radical into a hydroxy radical,
  - a conversion reaction of a haloalkyl radical into an alkylene radical,
  - a substitution reaction of a halogen atom by an amino
  - 25 radical,
  - a substitution reaction of a hydroxy radical by a halogen atom,
  - a reduction reaction of an esterified carboxy radical into a hydroxyalkyl radical,
  - 30 - an oxidation reaction of a hydroxyalkyl radical into an esterified carboxy radical,
  - an oxidation reaction of a hydroxymethyl radical into aformyl radical,
  - a resolution reaction of the racemic forms into resolved
  - 35 products,
  - a conversion reaction of a free, salified or esterified carboxy function, into a tetrazolyl radical,
- the said products of formula (IX<sub>8</sub>) thus obtained being in all the possible racemic, enantiomeric and diastereoisomeric

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isomer forms.

D A T E D    this       22nd       day of       December       1994.

ROUSSEL-UCLAF

By their Patent Attorneys:

CALLINAN LAWRIE

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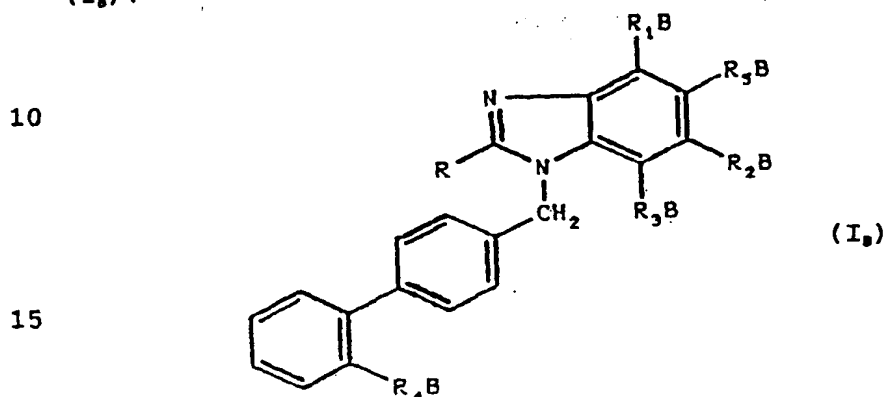
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RB

# ABSTRACT

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A subject of the invention is the products of formula (I<sub>9</sub>):



in which:

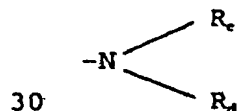
R represents an alkyl or alkenyl radical containing 3 or 4 carbon atoms,

R<sub>1B</sub>, R<sub>2B</sub>, R<sub>3B</sub> and R<sub>4B</sub> are such that:

either R<sub>1B</sub>, R<sub>2B</sub>, R<sub>3B</sub> and R<sub>4B</sub> represent a hydrogen atom,

or R<sub>2B</sub> and R<sub>3B</sub> are such that one represents a hydrogen atom and the other represents a hydrogen atom or a -CH<sub>2</sub>-O-R<sub>10</sub> radical, in

25 which R<sub>10</sub> represents a hydrogen atom or an alkyl or alkenyl radical containing at most 5 carbon atoms, or one of R<sub>2B</sub> and R<sub>3B</sub> represent the radical



and R<sub>10</sub> and R<sub>3B</sub> are such that one represents a hydrogen atom and the other is chosen from the radicals -OR<sub>6</sub>, -CO<sub>2</sub>R<sub>7</sub>, and -R<sub>11</sub>, in which radicals:

R<sub>6</sub> and R<sub>7</sub> represent a hydrogen atom or an alkyl or alkenyl radical containing at most 5 carbon atoms,

R<sub>11</sub> is chosen from the group formed by:

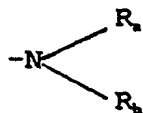
a) alkyl radicals having at most 4 carbon atoms, optionally substituted,



b) linear or branched alkenyl radicals having 2 to 5 carbon atoms,

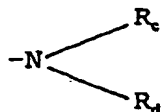
c) acyl radicals having 2 to 7 carbon atoms and the formyl radical,

5 d) the radical:



10 or at most two of  $R_{18}$ ,  $R_{28}$ ,  $R_{38}$  and  $R_{39}$  represents a hydrogen atom,

and the others are chosen from the radicals  $-\text{CH}_2\text{-O-}R_{10}$ ,  $-\text{OR}_6$ ,  $-\text{CO}_2R_7$ ,  $-\text{R}_{11}$  and the radical



15  $R_{18}$  represents a free, esterified or salified carboxy radical, a cyano radical or a tetrazolyl radical, or a  $-(\text{CH}_2)_m\text{-SO}_2\text{-X-R}_{12}$  radical in which  $m$  represents an integer from 0 to 4 and

20 either  $(-\text{X-R}_{12})$  represents  $\text{NH}_2$

or  $\text{X}$  represents a single bond, or the radicals  $-\text{NH-}$ ,  $-\text{NH-CO-}$ ,  $-\text{NH-}$  or  $-\text{NH-CO-}$  and  $R_{12}$  represents an alkyl, alkenyl or aryl radical,

the said products of formula (I<sub>9</sub>) being in all the possible 25 isomer forms, as well as the addition salts with acids and bases of the said products of formula (I<sub>9</sub>).

These products possess useful pharmacological properties which justify their use as medicaments.

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